Yale Pathology Tissue Services Center

A Pathology-based Central Tissue Resource Lab providing comprehensive tissue related services and material for investigators at Yale and beyond.

- Providing services as a shared resource of the Yale Cancer Center

Director: David L. Rimm, M.D.-Ph.D.

Mission: To provide the maximum amount and quality of human tissue for research at Yale University without impacting diagnostic quality, accuracy and safety in anatomic pathology.

Executive Summary:

Human tissue, collected by physicians for diagnostic purposes, is an extremely valuable resource for translational research. However, this resource is limited in amount and constricted in scope of use by the fact that it initially belongs to the patient from whom it was taken, and once collected, is an asset of the institution. Its diagnostic usage supersedes all other uses. This document represents a set of policies and standard operating procedures that would provide for optimal management of pathology resources including fresh, frozen, and fixed tissue, as well as tissue from the Yale Pathology Departmental Archives. In place of the traditional comprehensive tissue-banking model, this service maintains a limited pilot-type banking activity, and primarily relies upon prospectively acquired tissue and a distributive model of banking. The organizational structure and details of this model are outlined herein.

Underlying Premises:

- All tissue must be handled in strict compliance with HIPAA regulations, University research policies, diagnostic requirements and Hospital by-laws.
- Barriers to tissue use for research should be minimized as much as possible to promote basic and translational research at Yale and beyond.
- Tissue used for research should be made available as broadly as possible, but users must recognize and be prepared to assume the responsibilities and costs associated with all aspects of tissue procurement and management.
- Due to the scarcity of the resource, the distribution is overseen by an inter-department committee that can approve policy and adjudicate disputes related to allocations of scare resources.
- Due to the importance of tissue related information, the information delivery from clinical and pathology databases are also included in this distribution structure.

Definitions:

Diagnostic Tissue: This is the actual material used to render the diagnosis. This generally represents a single or series of tissue blocks. It is generally formalin-fixed and paraffin embedded material. It also includes the "frozen section control" or material that is fixed and processed after the completion of the frozen section procedure.

Excess Tissue: This refers to tissue received in the surgical pathology suite that is deemed by the resident, PA and/or attending pathologist to be unnecessary for the rendering of a diagnosis. This tissue will be either discarded or may be captured for research purposes.

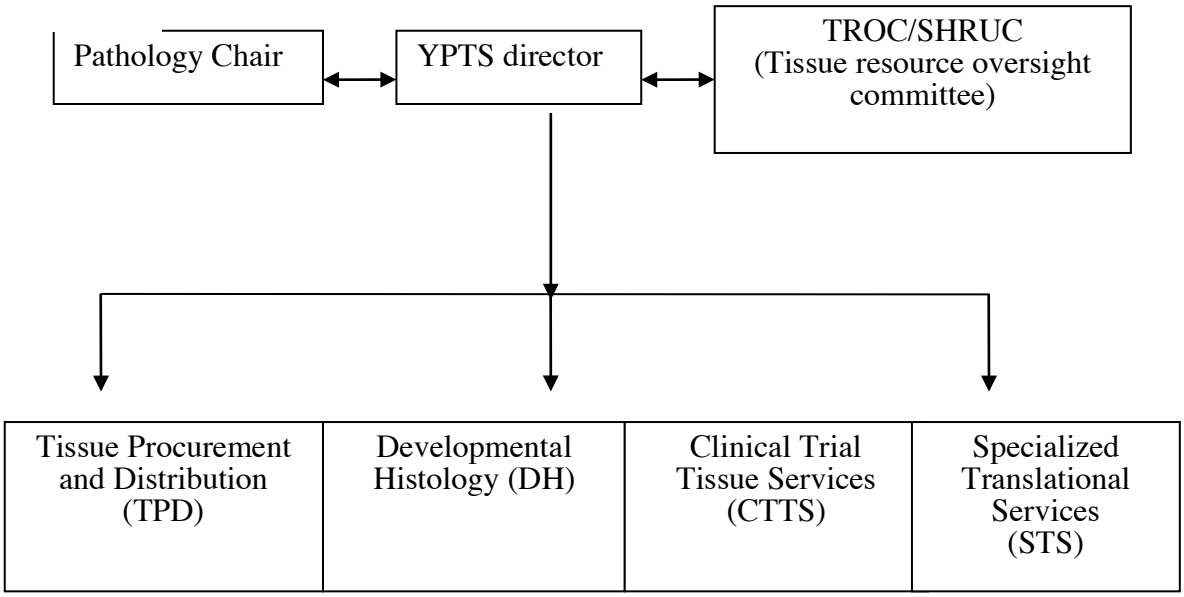
Protocol-Defined Tissue: This refers to tissue specifically taken for clinical trial protocols or other clinical studies that are previously approved by the Yale Human Investigation Committee (HIC). This tissue is managed in a manner stipulated by the protocol with over-sight by pathology as prescribed.

Tissue derived products: This term refers to DNA, RNA or protein made from tissue samples.

Structure of the Service:

The Yale Pathology Tissue Services would incorporate 4 branches including 1) Tissue Procurement and Distribution Services; 2) Developmental Histology, and 3) Clinical Trials Tissue Services 4) STS Lab (see figure 1). Each branch is governed by the Director, who reports jointly to the Chair of Pathology and to the Cancer Center director, as advised by the Tissue Resource Oversight committee appointed by the Dean. This committee will include representation from the Dean's office, and senior faculty from the Departments of Surgery, Medicine, Pathology, and other departments to be determined.

Figure 1



Service	**Medical Director**	**Technical Director**
TPD	Alexander Vortmeyer	Yalai Bai
DH	David Rimm	Lori Charette
CTTS STS	Alexander Vortmeyer David Rimm	 Veronique Neumeister

Identification and selection of human tissues (independent of processing)

The process of procuring annotated human tissue specimens for research purposes can be divided into two phases:

1. The identification and selection of excess tissues from Yale University tissue specimens, and
2. The processing of such tissues in a variety of ways that generate various added-value tissue products.

Cost recovery is based on the concept of a "***tissue unit***". One tissue unit is defined as follows:

A) Up to TEN 4-6 m tissue sections cut from a single paraffin block, *or*
B) A single tissue core (ranging from 0.6 to 4mm in diameter) taken from a paraffin tissue block, *or*
C) A 5 to 60 m thick frozen section (must be excess tissue; may not include diagnostic tissue) *or*
D) 50mg – 1gm of fresh frozen or custom-fixed tissue (must be excess tissue; may not include diagnostic tissue), *or*
E) Protocol-defined tissue that requires the review or oversight by the Dept of Pathology (independent of amount), or

F) A slice of a whole organ from autopsy (1 organ is equivalent to 10 tissue units), or
G) A curl from a single paraffin block 5 to 60 micron thick section placed in epi-tubes.

Each *tissue unit* has at a minimum annotation that includes the patient's age, sex, pathologic diagnosis, and tissue of origin. Additional annotation may also be available through the pathology informatics services including follow-up, treatment information, outcome information, whether a tumor is primary or recurrent, etc. The mechanism for obtaining this additional annotation is discussed below in the section related to Pathology-based patient data repository.

Tissue processing, including freezing, production of DNA, RNA or protein, tissue sectioning (frozen or fixed) and tissue microarray production are done by separate branches of the YPTS. These branches will apply further charges as part of the individual cost recovery policy of each division.

Additional charges are required for all materials sent outside of Yale:

A) Any tissue sent to a commercial party is charged 15% Yale Indirect costs and 6.35% sales tax
B) Any tissue sent outside Yale to other non-profit institutions is subject to the 15% Yale indirect charge.

Tissue Storage:

Tissues may be obtained through one of three pathways, known as the Pathways **A**, **B and C**.

***A** Pathway:* In this pathway collection and storage is a prospectively arranged excess tissue collection where a defined Principal Investigator (PI) user or user group prescribes collection and storage conditions and pays full fees, including Tissue Access fees, Tissue Storage fees and Tissue Preparation fees if required. This will be a significant financial commitment usually requiring grant funding or other mechanisms. Terms for a minimal number of specimens will be negotiable depending on demand and organ site. Negotiations will be conducted by the director of YPTS and overseen and approved by the TROC. These negotiations will be concluded in a contract, known as the "A Pathway Tissue Banking Contract" signed by the PI and the director of the YPTS indicating the responsibilities and privileges delineated below, and more completely in a sample contract in the appendix.

In this pathway the PI must work with YPTS staff to define a standard operating procedure (SOP) that completely describes the conditions of procurement, specimen handling, and storage. The PI must take full responsibility for all aspects of the stipulated tissue, including honoring embargo conditions, protecting collected data in accordance with HIPAA and HIC policies, and subsequent tissue sharing and distribution from storage. The PI is essentially a deputized subsidiary bank, potentially requiring other HIC approval as well as individual policies for application for usage and and application review .

The choice of database is open to the user, but the information must be collected in, or directly ported to caTissue. This software is required for tracking and monitoring of the tissue by the Dept. of Pathology. The A pathway users that are not currently using caTissue must commit usage with 6 months of inception of their banks.

It is assumed that as an "interested party", optimal conditions will be met for storage, sharing and distribution. No diagnostic tissue will be collected via this pathway. As a deputized tissue bank of the program, PI's using this route must agree to make unused tissues collected under this Pathway available to other investigators through Pathway B of the Program. No tissue procured through Pathway A may be redistributed to any party beyond the group defined by the PI of the A Pathway bank in the A Pathway Banking Contract, except through pathway B as managed by the TPD branch of YPTS.

***B** Pathway:* For new investigators or others with insufficient funding or others doing pilot studies, tissue may be obtained via the **B** pathway. Excess tissue will be procured by the Tissue Procurement and Distribution (TPD) Facility as per a standard TPD operating procedure (see appendix) using an SOP constructed by the investigator and the TPD staff. In addition, access can be provided to a previously established pilot tissue collection. For example, there may be a collection of a maximum of 50 breast cancers in this pilot bank, from which a maximum of 25 may be drawn by a pilot user. The TPD director will determine the types and numbers of specimens to be maintained in the pilot bank, subject to approval of the YPTS director and the TROC. Unlike the **A** pathway where a prescribed number of specimens are obtained, B pathway materials may be purchased on a per specimen basis for a single fee that includes access and preparatory changes (see appendix for cost recovery program). Users would not be able to stipulate collection conditions or availability. No diagnostic tissue would be present in this collection, and all material would be past its embargo date.

***C** Pathway:* In rare cases, a large organization may wish to sponsor collection of specific specimens. They may wish to establish a protocol and series of SOPs that require increased staffing due to needs that exceed typical tissue collection. For example if special consent is required or if patient interaction to draw blood prior to surgery is required, then these clients would be offered **C** pathway services. In the **C** Pathway, the client negotiates an overall support fee for a specified period of time with the director of YPTS. The support fee with be derived based on the SOPs requirements. The support fee is designed to provide added service to the client, beyond standard tissue acquisition. It is negotiated to provide full cost recovery for the added services. Since services may be less tightly tied to specimens, no per specimen access fee is charged. Rather a target number of specimens over the period of the contract is included in the contract as a deliverable, with the caveat that the number may not be achievable if the surgical resections are insufficient . **C** pathway budgets and expenditures by YPTS related to the collection efforts are at the discretion of YPTS directors and staff.

Embargo and Patient Safety:
To prevent tissues from being used in a manner that jeopardizes patient care, an embargo policy is in place. This means tissue must be held in storage prior to research use for a time period dependent on tissue type, as outlined below:

YPTS Embargo Time Table:

Tissue Type	**Time**
Frozen Tissue	one month after sign out
Fresh Tissue (for cell culture)	none
Formalin Fixed Paraffin Embedded Tissue	one year from accession date

*note, this timing is in compliance with CAP guidelines since only excess tissue is used for research. Thus is it critical that SOPs carefully define minimum sizes of lesions from which fresh tissue can be taken and that PAs or Pathologists participate is the selection of excess material.

Tissue Access Priority:
Excess tissue will be available on a first come, first serve basis. A priority date is obtained by completion of a valid, signed and approved **A** Pathway Collection Banking Contract filed with the director of YPTS and the Chair of Pathology. Model agreements will include complete SOPs that carefully define not only tissue procurement procedures, but also complete plans for storage, databasing, and tissue sharing for users both within, and outside of the PIs group. The choice of database is open to the user, but the information must be collected in, or directly ported to caTissue. This software is required for tracking and monitoring of the tissue by the Dept of Pathology. **A** pathway users that are not currently using caTissue must commit usage with 6 months of inception of their banks or be willing to deliver complete tracking spreadsheets of the contents of their banks on demand to the director of YPTS.

Tissue collected for a specific PI (or group) is not exclusively the property of that group and may be distributed to other users via the **A** pathway user or the **B** pathway pilot bank, depending on the amount of tissue collected in each specific instance. These decisions may be made at the surgical bench under the direction of Pathology Assistants at case intake. Unused tissue stored by an "A" user may also be subject to recall for use in the "B" pathway if needed. When multiple investigators are interested in the same type of tissue samples, attempts will be made to notify both PIs to attempt to have them determine the optimal collection schema that best suits both needs. Disputes over tissue or conflicting needs for scarce resources will be adjudicated by the TROC. In addition A and C pathway collecting PIs are encouraged to name an oversight committee for prioritization and distribution of tissues collected under their SOPs. They are further encouraged to include YPTS staff on these committees. The decisions of these committees are subject to the oversight and jurisdiction of the Tissue Resource Oversight Committee to ensure equitable distribution of tissue independent of funding mechanisms.

Diagnostic Tissue Procurement:
Tissue that has been used for diagnoses, but is approved for secondary research use either by direct patient consent, by a waiver of informed consent, or by other HIC approved mechanism is generally available only as formalin-fixed paraffin embedded tissue. All blocks containing this type of tissue are maintained in the Yale Pathology Archives and may be accessed for research purposes after the embargo period. Users may access this tissue either as tissue microarrays or as whole sections. Array usage is encouraged, as it extends the tissue resource. However whole sections may be requested and will be provided in a manner to minimize exhaustion of any tissue block. Diagnostic tissue can only be accessed via the Developmental Histology or Clinical Trials Tissue Services division of YPTS. Diagnostic tissue should not be cut to exhaustion to preserve material for unanticipated future diagnostic usage. If any user wishes to use an entire histology block, this tissue type should be collected prospectively using the **A** pathway mechanism for fresh tissue, then processed by the Develomental Histology division of YPTS.

Secondary Transfer of tissue:
Clients, whether academic or commercial, who obtain tissue from YPTS are not authorized to secondarily transfer the tissue outside their collaborative network to third parties for sale or otherwise. Agreement with this policy will be conveyed and certified by client signatures on quotes or invoices.

Policies by Division:
The allocation of the overall budget of the YPTS to the various subdivisions will be determined by the director. The resources available to the program from grant or service

income will be allocated to the various divisions so as to maximize the overall effectiveness of the YPTS. The policies established for cost recovery, service priority and operating protocols, for each service will be subject to review by the YPTS director. The YPTS budget will include:
1. All direct costs of operating the program (supplies, personnel, space, and equipment)
2. A negotiated fraction of support for procurement personnel in gross cutting room.
3. Informatics support of the tissue bank and block library;
4. Informatics support of the tissue database, to be provided through the Pathology informatics program;
5. Repayment to Pathology for subsidies received (for accrued deficits)
6. An allocation to Pathology as a fraction of gross operating revenues of the program to cover indirect expenses (to be determined).

Appendices:

1. The Policy Statement and Fee Schedule for the Tissue Procurement and Distribution Services
2. The Policy Statement and Fee Schedule of the Developmental Histology division.
3. The Policy Statement and Fee Schedule of the Clinical Trials Tissue Services

References relevant to policy:

1. Charo RA. Body of research--ownership and use of human tissue. N Engl J Med 2006;355(15):1517-9.

2. Schmidt C. Tissue banks trigger worry about ownership issues. J Natl Cancer Inst 2006;98(17):1174-5.

3. van Diest PJ, Kummer JA, Voest EE. Re: Tissue banks trigger worry about ownership issues. J Natl Cancer Inst 2007;99(3):253.

YPTS Fresh/Frozen Tissue Procurement and Banking Facility
Fee Schedule and Policy Statement

The Yale Tissue Procurement and Distribution Facility (YTPDF)

Director: Alexander Vortmeyer, M.D.

Mission Statement:

The mission of this division is to maximize the access of human tissues to translational investigators by providing high quality annotated fresh and frozen human tissue to Yale and other users.

Underlying Premises:

• All tissue must be handled in strict compliance with HIPAA regulations, University Research Policies, Pathology Department diagnostic requirements and Hospital by-laws.
• Barriers to tissue use for research should be minimized as much as possible to promote translational research at Yale.
• Tissue used for research should be made available as broadly as possible, but users must recognize and be prepared to assume the responsibilities and costs associated with all aspects of tissue procurement and management.
• Due to the scarcity of the resource, the distribution should be overseen by an inter-department committee that would approve policy; recommend cost recovery policy, and adjudicate disputes related to allocations of scare resources.
• Due to the importance of tissue related information, the information delivery from pathology data archives are also included in this distribution structure.

Underlying operational model:

The tissue procurement and banking module is a branch of the Yale Pathology Tissue Services (YPTS). The service relies upon prospectively acquired tissue and on a distributive model of banking. The service includes access to a previously established pilot tissue collection.

Investigator tissue access:

Tissues may be obtained through one of three pathways, known as the Pathways ***A, B*** and ***C***.

A or C *Pathway:* In this pathway a defined Principal Investigator (PI) user or user group (UG) prescribes collection and storage conditions and pays full fees, including Tissue Access fees, Tissue Storage fees and Tissue Preparation fees if required. The tissue storage function will be deputized to the PI/UG, and will be coordinated and supervised by YPTS. This pathway will require a significant financial commitment usually relying on grant funding or other mechanisms from the PI/UG. Terms for a minimal number of specimens will be negotiable depending on demand, organ site and the amount of Pathology oversight and manpower required. Negotiations will be conducted by the director of Yale Pathology Tissue Services and overseen and approved by the Tissue

Resource Oversight Committee. In this pathway the PI/UG must define the conditions of procurement and storage and takes full responsibility for all aspects of the stipulated tissue, including honoring embargo conditions and subsequent tissue sharing and distribution from storage. All data related to curation of this material must be entered into the CaTissue database, which will allow YPTS to oversight and coordinate inventories in the distributed banks, with the PI/UG acting essentially as a deputized subsidiary bank. Alternatively, they may provide full database information on request by the director of YPTS. Pathway ***A*** or *C* users may require full HIC "banking" type approval, or they may be able to be covered by the YPTS banking protocol, depending on the individual protocol used. It is assumed that as an "interested party", optimal conditions will be met for storage, sharing and distribution. No diagnostic tissue will be collected via this pathway. As a deputized tissue bank of the YPTS program, PI's using this route must agree to make unused tissues collected under this Pathway available to other investigators through Pathway ***B*** of the Program. No tissue procured through Pathway ***A*** may be redistributed to anyone not approved as a primary user or direct collaborator. Tissue distributed to any outside party must proceed through pathway B as managed by YPTS.

B *Pathway:* For new investigators, any researcher doing pilot studies or others with insufficient resources for A pathway type usage tissue may be obtained via the ***B*** pathway. Excess tissue will be procured by the Tissue Procurement and Distribution (TPD) Facility as per TPD standard operating procedure; in addition, access can be provided to a previously established pilot tissue collection. For example, there may be a collection of a maximum of 50 breast cancers in this pilot bank, from which a maximum of 25 may be drawn by a pilot user. The TPD facility director will determine the types and numbers of specimens to be maintained in the pilot bank, subject to approval of the YPTS director and the TROC. Unlike the ***A*** pathway where a prescribed number of specimens are obtained, B pathway materials may be purchased on a per specimen basis for a single fee that includes access and preparatory changes. Users would not be able to stipulate collection conditions or availability. No diagnostic tissue would be present in this collection and all material would be past its embargo date.

Access Priority:

Tissue access will be offered on a first come, first serve basis. A priority date is obtained by completion of a valid filing with the Technical Director of the facility. The turn-around time for tissue samples will thus be determined by workload and staffing. In addition A and C pathway collecting PIs are encouraged to name an oversight committee for prioritization and distribution of tissues collected under their SOPs. They are further encouraged to include YPTS staff on these committees.

Quality Control:
The current practice of the facility is to use tissue sections for quality control purposes. Slides are H&E stained and reviewed by a pathologist to determine preservation and histological features of the tissue. Additional quantitative quality assessment pertaining the proteome, transcriptome and genomic DNA preservation will potentially be available if prescribed, under the ***A*** Investigator access pathway, for specific tissue collections. All available quality control information will be incorporated in the tissue annotation data set.

Inventory of tissue:

caTissue is the application responsible for the core handing, tracking and distribution of specimens within the YPTS biorepositories. *caTissue*, a product of the NCI cancer Biomedical Informatics Grid (caBIG) effort, will also provide the infrastructure for the

integration of clinical and pathological tissue annotation data. Specimen's retrieval will, when applicable, also be facilitated by the use of RFID (radio frequency identification) and barcode tagging. Entry of tracking and annotation information of tissues distributed to subsidiary banks through the ***A*** pathway will be decentralized to the deputy banking units, under the coordination and supervision of the YPTS. Tissues related information will be easily accessible to all authorized users through the web *caTissue* interface and the presence of RFID or barcode tags will allow control of tissue identification and facilitate tissue retrieval.

Annotation:

Each tissue unit is distributed with an annotation data set downloadable by facility staff from *caTissue*, Pathology databases or CaDR (the Yale Cancer Data Repository). The *caTissue* Clinical Annotation Engine is the main web-based application responsible for providing access to annotation of specimens within YPTS biorepositories. The *caTissue* Clinical Annotation Engine allows uniform access to the distributed repositories and guarantees the standardization and protection of the research data. Yale users may obtain password-protected direct access to *caTissue* through the YPTS staff. However, they are not required to do so. If desired, they will receive a standard annotation in a flat text file with each tissue distribution event. Annotations of tissues beyond that available from the facility may be available from other investigators either by collaboration or by license.

Embargo and Patient Safety:
To prevent tissues from being used in a manner that jeopardizes patient care, an embargo policy is in place. This means tissue must be held in storage prior to research use for a time period dependent on tissue type, as outlined below:

YPTS Embargo Time Table:

Tissue Type	**Time**
Frozen Tissue	one month after sign out
Fresh Tissue (for cell culture)	none
Formalin Fixed Paraffin Embedded Tissue	one year from accession date

*note, this timing is in compliance with CAP guidelines since only excess tissue is used for research. Thus is it critical that SOPs carefully define minimum sizes of lesions from which fresh tissue can be taken.

Furthermore, to assure patient safety and increase tracking options for tissue, whenever fresh tissue is taken for research purposes, notation will be made in the gross description. The text is to be determined and defined in the SOP for each collection procedure.

Tissue Access:

The process of procuring annotated human tissue specimens for research purposes can be divided into two phases:

1. The identification and selection of tissues from surgical pathology specimens
2. The processing of such tissues in a variety of ways that generate various added-value tissue products.

Pricing is based on the concept of a "tissue unit". One tissue unit is defined as follows consistent with overall YPTS policy as described on page 3 above:

A) Up to ten 4-6 μm tissue sections cut from a single paraffin block, or
B) A single tissue core (ranging from 0.6 to 4mm in diameter) taken from a paraffin

tissue block, or
C) A 5 to 60 μm thick frozen section (must be excess tissue; may not include diagnostic tissue) or
D) 50mg – 1gm of fresh frozen or custom-fixed tissue (must be excess tissue; may not include diagnostic tissue), or
E) Protocol-defined tissue that requires the review or oversight by the Dept of Pathology (independent of amount), or
F) A whole organ from autopsy (1 organ or large slice is equivalent to 10 tissue units)
G) A curl from a single paraffin block 5 to 60 microns thick section placed in epi-tubes.

Each tissue unit has at a minimum annotation that includes the patient's age, sex, pathologic diagnosis, and tissue of origin. Additional annotation may also available, depending on the nature of the specific tissue collection, through the pathology informatics services including follow-up, treatment information, outcome information, whether a tumor is primary or recurrent, etc.

The price for tissue unit is as follows:

Pathway A and C: PI or UG distributed banking

Terms and pricing of the distributed banking tissue collection will vary depending on the tissue nature, additional annotation etc. Negotiations for the terms for these collections will be conducted by the director of Yale Pathology Tissue Services and overseen and approved by the Tissue Resource Oversight Committee. Negotiations will reflect the value of tissues on the basis of the tissue access fee and the value of the banking services provided by the A Pathway users.

Pathway B: New investigators or others with insufficient funding or others doing pilot studies

1. Discount due to Cancer Center Members or SPORE members to be determined on an annual basis (as a function of the percentage of financial contribution to YPTS).

Additional charges are required for all materials sent outside of Yale:
A) Any tissue sent to a commercial party is charge 15% Yale Indirect costs (overhead) and 6% sales tax
B) Any tissue sent outside Yale to other non-profit institutions is subject to the 15% Yale indirect charge.

Secondary Transfer of tissue:
Clients, whether academic or commercial, who obtain tissue from YPTS are not authorized to secondarily transfer the tissue to third parties for sale or otherwise. Agreement with this policy will be conveyed and certified by client signatures on quotes or invoices.

Developmental Histology Facility Fee Schedule and Policy Statement

The Developmental Histology Facility (DH)
(a division of Yale Pathology Tissue Services)

Director: David L. Rimm, M.D.-Ph.D.

Mission Statement:

The mission of the research histology Developmental Histology Facility is to provide

1. Timely high quality research histology services to the Yale community and beyond
2. Access to tissue services from Yale Pathology archives
3. To maximize the value of the resources in the Yale Pathology Tissue Archive.
4. To provide Tissue Microarrays to assess multiple tissue samples

Animal tissues

For routine animal tissue processing, the investigator provides fixed tissue within standard tissue cassettes. Tissue dissection is the responsibility of the investigator. The tissue will normally be placed in the research histology processor that same day and embedded the next morning. Special embedding instructions will be honored insofar as they are technically possible.

Frozen sectioning of animal tissues is done by research histology staff

Turnaround time for cutting and staining routinely processed animal tissues must be less than one week depending on size and technically difficulty of the request. When this turnaround time cannot be met in greater than 90% of cases, tissue blocks will be sent to an outside laboratory designated by the director until the goal is met.

Human tissues

Investigators who perform biopsies on human subjects as part of an HIC approved clinical research project (protocol-defined tissue) may have tissues processed in research Developmental histology. The Yale HIC approved consent form for such biopsies must clearly state that no Yale pathology diagnosis will be available on such tissues.

De-identified human tissue samples are available from research histology with no additional HIC approval. These will be provided from the research paraffin cassettes or from frozen tissue as available. A listing of cases for which research material is available is maintained in research histology. If no suitable tissue is available from the research tissue archives, the Yale pathology paraffin archives may be used. The tissue coordinator will provide the case numbers. The research histology staff will pull and refile these blocks as needed. These tissues provided to investigators will have no identifier on them other than tissue type. Additional tissue from the same block will not be available.

For cases which are labeled with the Yale pathology number, a Yale HIC approval is required. The Yale HIC number will be included in the order database.

In no cases will blocks from Yale pathology archives be cut through without approval from the director of developmental histology. In no case will Yale pathology archive blocks be released to investigators. For long term research projects involving the creation of a unique patient cohort, segregation of tissue blocks into a physically

segregated tissue archive at the discretion of the facility. Projects with segregated material (sub-archives) include tissue microarray projects and others at the discretion of the director of the facility.

Frozen tissues

Investigators are encouraged to have tissue sections prepared from frozen tissue from the tissue bank (either as frozen sections or as portions thawed and conventionally processed) prior to use in order to ensure the nature of the tissue provided. Investigators must have pathology collaborators to help them with this process. Otherwise, the director of research histology will assist them in finding a collaborator that will examine those sections.

Immunohistochemistry:

Immunohistochemical projects are performed on both human and animal tissues. For human tissues, the services offered include CLIA lab approved services and Research Use Only (RUO) services. The labs that execute the work will be in accordance with the work requested and the policies of the Department of Pathology. For human studies, tissue controls can be provided within the guidelines as described above for accessing human tissue. Protocols for staining (automated vs manual staining) and control selection must be worked out in advance or can be done by the facility and may require separate negotiated contracts. When protocol development is required, users will be required to cover the cost of test slides, test reagents, and staining costs. For example, titering a new antibody may require 5 slides with different antibody concentrations. The user would be billed for 5 immunostains (see below).

TMA construction policy:

Construction Pathways and Ordering:
There are two pathways for array construction.

Pathway A arrays: If a user anticipates that they will need a large number of sections or a high proportion of an array, or if a user would like to maintain control over the distribution of the array, then they must commission it and pay for it at the rates shown below. They may then stipulate the map of the array and purchase the entire block or as many sections as they would like at $20 per section. If other users wish to purchase sections from this array, the commissioning investigator will be sought and they will have the rights to order more sections, prior to filling the order of the other requesting user. In the case of commercial users commissioning slides, one third of the array is reserved for Yale or Academic users, so they may only obtain and control an average maximum of 90 slides from each block. Blocks containing Yale Tissue are maintained by the TMA facility.

Pathway B arrays: If a user only anticipates needing a few slides from an array, they may not desire or be fiscally able to commission array. In this case, the array may be produced by the facility and the user may purchase slides at the price shown above for blocks in inventory. No investigator will have the privileges associated with array construction and the Path B requesting user will not be notified if other users want to purchase slides from this type of array. The "per slide" charge is fixed strictly as a function of the number of spots on the array (there is no volume discount). Path B arrays will only be constructed if the facility judges that it will be able to recoup construction cost by provision of slides to multiple users. This policy allows unfunded investigators

equal access to the resources produced by the facility. Blocks containing Yale Tissue are maintained by the TMA facility.

Pathway C Arrays: The facility may be engaged by outside sources to produce arrays. In this case it is the responsibility of the client to provide the tissue blocks and annotated slides for array production. This tissue will not be charged the tissue unit charge, but otherwise be subject to all other fees of array construction. Unlike the A and B pathways, these blocks may be released by the facility to the client, as per arrangement with the client. A block relinquishing fee will be assessed since cost recovery will not be accrued from block sectioning. Quotations for estimated costs for C pathway arrays will be provided upon client request.

Quality Control:
The current practice of the facility is to use every 10th slide for quality control purposes. This slide is H&E stained and reviewed by a pathologist to determine the number of valid cores. This data is maintained with the array distribution data. When the percentage of valid cores dips below 75%, then slides will no longer be routinely distributed (this generally occurs between cuts 70 and 100). If slides are received by users that are of poor quality (>25% spots missing) or affected by another anomaly, the slide will be replaced, at no charge, by the facility. The judgment of quality will be at the discretion of the staff of the facility.

In the case of large arrays, these "high cut number" slides may still be useful and have value albeit less than the original cohort. Thus these are still available at the same fee structure defined above and generally will not be used as test arrays or discarded until the level of valid cores dips below 50%. These "high cut number" slides are distributed "as is" with no opportunity for replacement due to poor quality. They may also be purchased at the "per spot" fee, on the basis of the number of spots on the nearest QC slide.

Construction Priority:
Arrays will be constructed on a first come, first serve basis. A priority date is obtained by completion of a valid TMA construction order form and filing with the Technical Director of the facility. The turn-around time for arrays will thus be determined by work load and staffing.

Arrays made for a specific investigator are not exclusively the property of that investigator and may be distributed to other users. However, attempts will be made to notify the initiating investigator when sections are requested from the block they commissioned. The other user will be encouraged to contact and collaborate with the commissioning investigator. The other user will be required to pay full construction fees if the original user exhausts the array. Otherwise the other user will pay for the array at the rates above for facility inventory.

Inventory of Blocks:
The facility draws Yale Pathology blocks from the Pathology archives for use in arrays. Once a block is removed from the archive and selected for use in an array, it is maintained in a sub-archive. These blocks are not returned to the Pathology Department Archives, but they are easily retrievable by database search. They are maintained in array numbered boxes within the facility. These blocks will be cored and returned to their source within a time scale agreed upon at the time of array design and ordering.

Annotation and Maps:

Each array is distributed with an array map that is downloadable by facility staff from AQUAmine. AQUAmine is a web-based interface for maps and data associated with TMAs. Yale users may obtain password-protected direct access to AQUAmine through the TMA staff. However, they are not required to do so. If desired, they will receive an electronic map with standard annotation in a flat text file with each array distribution event. Annotations of arrays, beyond that available from the facility, may be available from other investigators either by collaboration or by license.

Cell line controls in TMAs:
Often times it is valuable to include cell lines or purified protein controls in TMAs. Investigators may provide their own cell line or protein blocks for inclusion. A protocol for preparation of cell line blocks can be downloaded from the facility web site. Inclusion of cell line cores is billed at the standard array rate, but there is no tissue access charge. Some standard cell lines may be available from the TMA facility, produced by the TMA facility. These may be ordered through the facility, but are billed using the "tissue access" fee, as well as the arraying charge.

Many immunostains (especially for human tissue) are routinely available along with control tissues. The director and technical director will maintain stocks of commonly used reagents. This stock will include commonly requested primary antibodies and commonly used secondary reagents. A list of these reagents will be available from the facility. Reagents that are not on the list and unusually expensive reagents must be provided by the client investigator. This may include both primary and secondary antibody reagents**. Efforts will be made to work with clients to help them optimize their IHC protocols. If extensive efforts are required for antibody validation, clients will be billed at $40 per hour for this service (to be negotiated at the time of service order).**

For fees for processing/ sectioning/ staining for laser capture microdissection, "PCR safe sections", plastic sections, TUNEL staining and other specialized projects, contact the director of developmental histology research histology. Special assays will be billed on the basis of the costs plus the hourly charge.

Quotes are available on request and are required for orders larger than $1000.

Additional charges are required for all materials sent outside of Yale:
A) Any tissue sent to a commercial party is charged 15% Yale Indirect costs (overhead) and 6% sales tax
B) Any tissue sent outside Yale to other non-profit institutions is subject to the 15% Yale indirect charge.

Secondary Transfer of tissue:
Clients, whether academic or commercial, who obtain tissue from YPTS are not authorized to secondarily transfer the tissue to third parties for sale or otherwise. Agreement with this policy will be conveyed and certified by client signatures on quotes or invoices.

YPTS Clinical Trials Tissue Services
Fee Schedule and Policy Statement

The Yale Clinical Trials Tissue Services (YCTTS)

Director: Alexander Vortmeyer, M.D.

Mission Statement:

The mission of this division is to maximize the access of human tissues to investigators participating in correlative science or companion diagnostics aspects of clinical trials by providing high quality formalin-fixed, paraffin embedded tissue block cores or tissue slides to users and correlative science committees for clinical trials at Yale and around the world.

Underlying Premises:

- All tissue must be handled in strict compliance with HIPAA regulations, University Research Policies, Pathology Department diagnostic requirements and Hospital by-laws.
- Barriers to tissue use for research should be minimized as much as possible to promote translational research at Yale.
- Due to the scarcity of the resource, the distribution should be overseen by an inter-department committee that would approve policy; recommend cost recovery policy, and adjudicate disputes related to allocations of scare resources.

Underlying operational model:

Tissue is often requested for inclusion in a clinical trial, or for the correlative science associated with a clinical trial. This tissue is often requested in IRB/HIC approved protocols with specific requirements for FFPE tissue sections or tissue blocks. In order to meet this need CTTS offers the recut slides, at thickness requested or 4mm tissue cores, re-embedded into a labeled tissue block.

For each request, a standard form must be completed by the requesting investigator. The form (see example in appendix below) contains ordering and shipping information and charging instructions. The form may establish a "standing order" but must be established as a standard operating procedure approved and signed by requesting investigator and the Technical and Medical directors or the CTTS. The CTTS will keep a log book of all SOPs with signatures and per unit price quotes, as per charging structure for below for cost recovery.

Tissue Access Fee: surcharge for Yale Pathology human tissues
The standard tissue access fees for excess tissue obtained by Yale Pathology are as follows:

Pricing is based on the concept of a "tissue unit". One tissue unit is defined as follows:

A) Up to ten 4-6μm tissue sections cut from a single paraffin block, or
B) A single tissue core (ranging from 0.6 to 4mm in diameter) taken from a paraffin tissue block, or
C) A 5 to 60 μm thick frozen section (must be excess tissue; may not include diagnostic tissue) or
D) 50mg – 1gm of fresh frozen or custom-fixed tissue (must be excess tissue; may not include diagnostic tissue), or
E) Protocol-defined tissue that requires the review or oversight by the Dept of Pathology (independent of amount), or
F) A whole organ from autopsy (1 organ or large slice is equivalent to 10 tissue units), or
G) A curl from a single paraffin block 5 to 60 microns thick section placed in epi-tubes.

Each *tissue unit* has at a minimum annotation that includes the patient's age, sex, pathologic diagnosis, and tissue of origin. Significantly more information may be available.

Additional charges are required for all materials sent outside of Yale:
A) Any tissue sent to a commercial party is charge 15% Yale Indirect costs (overhead) and 6.35% sales tax
B) Any tissue sent outside Yale to other non-profit institutions is subject to the 15% Yale indirect charge.

Billing

The research developmental histology… (FileMaker) billing database provides billing information for routine histology, immunohistochemistry (regardless of lab which performs the work), human tissue fees, and fresh tissue access fees. The database provides sufficient information for the business office to direct the funds to the appropriate account.