

# NLST-ACRIN REMNANT TISSUE

## MANUAL OF PROCEDURES

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## 1. INTRODUCTION

The National Lung Screening Trial is a multi-center, randomized, controlled trial in which low-dose helical chest computed tomography (CT) will be compared with chest X-ray (CXR) to determine which screening test will result in fewer lung cancer deaths among individuals at high risk of lung cancer. The NLST-ACRIN specimen biorepository has collected specimens from roughly 10,000 participants in both the CT and CXR arms, and will be a key national resource for determining lung cancer etiology and the molecular markers of early lung cancer.

ACRIN is being funded through the NCI I2 mechanism for the collection of resected tissues from all participants in the NLST who have had a lung cancer resected. The NLST-LSS will similarly be collecting resected tissues from lung cancer participants. This collection provides increasing opportunities for the study of questions relevant to tumor molecular biology, and specifically, the contributions of genetic and proteomic factors that initiate or sustain cancer and metastases and for relating blood, urine, or sputum-based markers to the molecular signatures of the primary tumors.

### 1.1 Study Objectives

The main objective of the NLST remnant tissue collection is to answer critical questions about cancer etiology. This collection is unique because:

1. The tissue is obtained from a sample of extremely well characterized individuals.
2. Many participants will have other available biospecimens obtained at the screening visits, potentially prior to the diagnosis of lung cancer, on which ancillary and complementary studies can be performed.
3. Serial pre-diagnostic samples allow for the study of relationships between blood, urine and sputum-based early detection markers and tissue molecular characteristics.

The specific objectives of the NLST specimen collection efforts are:

1. Collect pathology samples to provide opportunities for research relating risk factors to histological and molecular-pathologic sub-types of lung cancer.
2. Study tissues of different stage to enhance the understanding of markers for lung cancer etiology and early detection.
3. Study tissue characteristics relative to epidemiological observations.
4. Study the influence of environmental exposures, hereditary factors, and other types of exposure on molecular lesions.

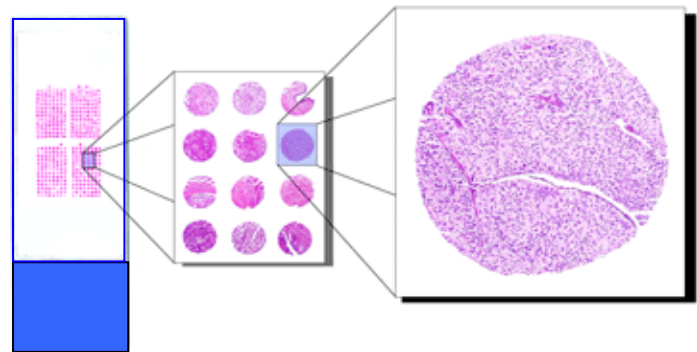
### 1.2 Scientific Background

The creation of an archive of resected lung cancers will richly augment the existing serial biosamples obtained on participants at the screening visits and will promote identification of the most significant molecular phenomena associated with lung cancer.

The remnant tissue archive will be based on tissue microarray (TMA) technology. In this method, minute tissue cores are removed from hundreds of different primary tumor blocks and subsequently brought into one recipient paraffin block that can contain up to 500 individual cores. Sections from such array blocks can then be used for simultaneous *in situ* analysis of hundreds of primary tumors at the DNA, protein, and potentially RNA level. TMAs are suited for all analyses that can be done *in situ*, including immunohistochemistry (IHC), fluorescence *in situ* hybridization (FISH), and potentially RNA *in situ* hybridization (RNA-ISH).

The major prerequisite for TMA construction is a large collection of well characterized tissues—as is the case with the NLST participants, in whom detailed demographic data, health information, smoking histories and exposures to other known carcinogens

have been collected. All lung cancers will have been characterized by location, histology and grade, and clinical pathological stage at diagnosis. All treatments will be recorded as well as disease free interval and locations and kinds of tumor recurrence.



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There are numerous advantages to TMA technology over the banking of standard tissue paraffin blocks:

- Amplification of the limited tissue resource: Standard histologic sections, after use for primary diagnosis, may yield material for a maximum of 100 assays. If this same block is processed for optimal microarray construction in which the primary paraffin block is cored multiple times (0.6 mm cores of minimum 2 mm depth), duplicate and triplicate sets of TMAs can be created to effectively amplify the limited tissue resource.
- Experimental uniformity: With TMA technology, each of the 400-500 tissue samples on a single slide are treated in an identical manner, using identical reagent concentrations, incubation times, temperatures, and other experimental conditions. This is in contrast to individual histologic slides for conventional formalin fixed paraffin embedded material, in which there may be substantial slide to slide variability during processing.
- Decreased assay volumes: TMA analyses require only very small volumes of reagent to analyze an entire cohort.
- Preserves the original block: Typically, the original block must be returned to the donating institution, particularly if the tissue being requested is the most representative of the tumor. TMA cores are extremely small, do not destroy the parent block, and preserve the diagnostic utility of the block for future histologic analyses.

### 1.3 Tissue Types and Methods of Sampling Selection

Representative tissue cores from resected surgical specimens will be obtained based on annotation of targets (regions of interest) on a representative slide of the tissue block by a lung pathologist. The following tissue types are of interest:

- **Primary lung cancer.** Multiple cores will be obtained from each representative area of tumor histology and grade to capture the molecular heterogeneity within these regions.
- **Adjacent normal (or non-tumor) lung tissue.** Cores will be obtained from representative areas of non-malignant tissue, with the aims of sampling: normal adjacent lung parenchyma, non-tumorous proximal bronchus, non-tumor distal bronchiolar tissue, and pre-malignant lesions (such as dysplasia, atypical adenomatous hyperplasia).
- **Malignant lymph nodes.** Malignant lymph nodes that have been resected should be included in the request for tissue blocks, since the molecular signatures of metastases may differ from the primary tumor. Multiple cores will be obtained from these individual lymph nodes.
- **Normal lymph nodes.** Cores should be taken from uninvolved lymph nodes *if* cores were taken from involved nodes (to capture germ line DNA).
- **Resected metastases** will be available in a small percentage of participants. Any surgically resected metastatic lesions should be requested. Multiple cores will be obtained from these tumor metastases.

An H&E slide created from each paraffin block of resected tissue will be digitized on the Aperio system for annotation by a lung pathologist. The slide digitization system allows the pathologist to review the slide at low and high (20X to 40X) powers. Color-coded targets (regions of interest) will be digitally annotated on the slide, from which a thin film template can be created to guide the coring process. The digitized slides will be permanently archived. The anticipated duration of the tissue collection and building of the TMAs is 18 months.

## 2. SAMPLE SELECTION

### 2.1 Selection Criteria

The selection criteria for remnant tissue collection will include all participants in NLST:

- Who have a documented primary lung cancer *and*
- Whose primary lung cancer or lung cancer metastases have been resected.
- Signed a Remnant Tissue Consent Form (See Section 2.4 - "Informed Consent")

The ACRIN BDMC (Biostatistics Data Management Center) will provide a list of all confirmed lung cancers in a Remnant Tissue Selection List to each individual NLST site. For each confirmed lung cancer case, the site should collect the following documentation:

- Original pathology report. Procure ALL pathology reports, as there may be multiple reports if there were separate surgeries (e.g., initial mediastinoscopy for lymph node resection and thoracotomy for lung resection),
- Operative report(s) corresponding to the pathology report.

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It is possible that an NLST site will become aware of additional lung cancer cases that have not yet been recorded in the ACRIN database. In this case, consult with ACRIN Data Management and the lead administrator of the Resected Tissue Project before acting on these cases.

## 2.2 Contacting Pathology Departments/Laboratories

The Pathology Report documenting the diagnosis of primary lung cancer will identify the source pathology laboratory. The site should contact the pathology laboratory to establish a relationship and to procure contact information, including: the name, phone number, e-mail address, fax number, and shipping address of a contact person at the laboratory for specimen collection.

The lending pathology laboratories may require specific documentation before the release of surgical tissues, including:

- Signed informed consent
- Signed Authorization to Release Surgical Material
- HIPAA authorization (or equivalent form prior to HIPAA enactment)
- Their own institutional forms
- Any combination of the above
- No documentation

It is strongly recommended that sites contact the laboratories to determine exactly what they will require prior to making specific requests for tissues.

The site should also determine the pathology laboratory's policies on specimen loans, costs for requesting specimens, whether the lab is willing to grant permanent retention of the specimens or, if not, the maximum loan period permitted. The site should inform the lab of the available reimbursement rate for processing and providing tissues and the minimum loan period of three (3) months required to ensure adequate time for shipping and processing. Payment for requests, if required by the pathology laboratory, should be managed by the site in agreement with the pathology laboratory.

Information regarding the laboratory's procedures for specimen preservation and all contact information should be obtained and entered into the **NLST Remnant Tissue Tracking Excel File** that has been developed for use by the sites. The NLST Remnant Tissue Tracking Excel File template can be downloaded from the ACRIN web site under 6654 Protocol Specific Materials link at: <http://www.acrin.org>. All information entered in the NLST Remnant Tissue Tracking Excel File is for site use only. A site may opt to track pathology request and shipping information in another site-specific format. Please note that tracking methods *will be reviewed* by the ACRIN auditor in order to confirm that efforts to obtain specimens were initiated.

## 2.3 Confidentiality

The confidentiality of the identity of participants will be maintained. All collected information will be protected per ACRIN policies and procedures and federal regulatory guidelines. Access to study data will be limited to the NLST staff working on the study. All computer data will be maintained in a manner consistent with Title 21 Code of Federal Regulations (CFR Part 11). In addition, access to the data management system will be limited to designated staff through use of confidential login ID and password.

The data from this study will be maintained until 10 years following completion of the study or until no longer required for research. Data will be destroyed as required by the ACRIN Record Retention Policy and federal regulatory guidelines. Human research subjects are protected in accordance with Title 45 Part 46 and Title 21 CFR Part 50.

## 2.4 Informed Consent

Human research subjects are protected by informed consent procedures in accordance with Title 45 CFR Part 46 and Title 21 CFR Part 50. The remnant tissue consent form grants permission for study investigators to request and obtain surgical material, such as pathologic tissues, and to use those samples for research involving

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molecular studies on the development of lung cancer and/or for other diseases.

Some participants will already have provided written informed consent for the collection of remnant tissue collection using consent forms provided as Appendices in Protocol 6654 at the time of enrollment. Depending upon original site preferences, permission for remnant tissue collection may previously have been administered as part of the biospecimen consent form for the collection of blood, urine, and sputum specimens at the time of the annual screening examinations, or as an independent consent form.

If there are participants with potential remnant tissues who have *not* previously been approached to provided written informed consent for remnant tissue collection the site may approach their IRB to consider a waiver of consent under Title 21 CFR Part 56 section 56.109. Please contact the ACRIN Regulatory Department if guidance is needed in obtaining a waiver.

## 2.5 Participant Authorization to Release Surgical Material and HIPAA

ACRIN-NLST sites have administered a HIPAA authorization or notification (ACRIN template or local-IRB approved HIPAA release) to NLST participants at the time of randomization in accordance with their local IRB / institutional guidelines. Lending pathology laboratories may or may not accept this authorization when lending remnant tissue.

Some lending pathology laboratories may request additional authorization from the participant in order to release remnant tissue. They may have a specific Authorization Form that they will send to you or, if permitted by the lending pathology laboratory, you may use the template provided marked as Appendix II "Authorization to Release Surgical Material Template".

Participants selected for remnant tissue collection, where the lending pathology laboratory requires additional authorization, should mail the necessary materials to the participant prior to making a request for remnant tissue from the lending pathology laboratory. Please refer to your local IRB for further guidance regarding any additional requirements.

If applicable, mail the following to the participant and complete the following steps:

1. Personalized Authorization Cover Letter Template (Appendix I)
2. Authorization to Release Surgical Material (**Appendix II**), which requests participant permission for the named pathology laboratory to release pathology specimens and related health information and personal identifiers to the ACRIN-NLST or the proprietary authorization form from the lending pathology laboratory
3. A second duplicate Authorization to Release Surgical Material or proprietary authorization form from the lending pathology laboratory to be retained by the participant for their personal records
4. A self-addressed stamped envelope for enclosure of the signed authorization to be mailed back to the site
5. Review signed authorization, store it in the participant's ACRIN file, and document receipt in the remnant tissue tracking file with date of signature
6. Send all necessary authorizations to the lending pathology laboratory for release of the remnant tissue.

ACRIN-NLST sites must abide by regulations established by their local IRB when dealing with cases in which the participant is deceased. These cases will need to be reviewed individually to establish the possibility of obtaining Authorization to Release Surgical Material Remnant Tissue for collection where necessary.

If a participant is unable to sign and date the Authorization to Release of Surgical Material because of illness or other problems, the Authorization to Release Surgical Material can be sent to the participant's authorized representative or proxy for signature according to local IRB rules.

Only Participants for whom a signed Authorization to Release Surgical Material is required and obtained will be included in the remnant tissue process.

### 2.5.1 Non-Response Follow-Up for Authorization Form

If the site does not receive a signed Authorization Form from the participant or proxy within three (3) weeks of the first mailing, the site should initiate non-response follow-up efforts, as follows:

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1. After three (3) weeks with no response:
    - Up to two (2) phone call attempts to contact the participant or proxy
    - Re-mail the materials if needed
  2. After additional three (3) weeks with no response:
    - One (1) additional phone call attempt to contact the participant or proxy
    - Document non-response in the participant chart on the Non-Response Log: Request for Authorization (Appendix III).

### **3. REQUESTING SPECIMENS FROM LENDING PATHOLOGY LABS**

#### **3.1 Request Packets**

Once participant consent and authorization is established, the NLST site coordinator should assemble a request packet for each pathology laboratory. Specimens from multiple participants may be requested from a single pathology laboratory in one packet. Each request packet will include the following items (which are included as appendices to this MOP and are explained in detail in the following sections):

1. **Pathology Request Cover Letter (Appendix IV)** signed by the NLST Site Principal Investigator (PI) or designee.
2. **Pathology Specimen Collection—Request Form(s) (Appendix V)** that specifies the requested histologies. This will be used by the pathology laboratory to document release of the specimens or the reasons for which specimens were not provided.
3. Copies of the participant(s) **Authorization to Release Surgical Material (Appendix II)** or comparable authorization according to the pathology labs policies
4. **Pathology report** for all participants included in each pathology laboratory request.

These items are included as appendices to this MOP and are explained in detail in the following sections.

##### **3.1.1 Pathology Request Cover Letter**

The Pathology Request Cover Letter (**Appendix IV**) briefly explains the purpose of the request, how loaned specimens will be processed and returned to the originating pathology laboratory, and asks that specimens be mailed to the NLST site in the pre-addressed, postage-paid shipping containers.

##### **3.1.2 Pathology Specimen Collection—Request Form**

The Pathology Specimen Collection—Request Form (**Appendix V**) will be used by lending pathology departments to indicate the release of specific specimen types and their unique paraffin block identification, or to indicate problems associated with fulfilling the request. The NLST Site coordinator will be responsible for filling out the pertinent participant information at the top of the form and the Date of procedure for each block that is being requested before sending the form to the lending pathology laboratory. The form should be returned by the lending pathology laboratory to NLST sites along with specimen blocks, or returned alone to indicate barriers or reasons for refusal to provide tissues.

Note that a Pathology Specimen Collection—Request Form should be provided for *each* individual participant. Multiple forms may be included in a request packet if specimens from multiple participants are requested at one time. Also, a pathology laboratory may receive additional request packets through the year as the NLST site continues to identify participants with new lung cancer diagnoses. If a pathology laboratory does not return a filled out Pathology Specimen Collection Form, the site RA is responsible for filling out a “Note to File”. Please document if you received specimen(s) or not and the reason for not getting a returned form. A copy of the Note to File” should be retained in the participants chart.

##### **3.1.3 Authorization to Release Surgical Material**

The signed Authorization to Release Surgical Material (**Appendix II**) should be attached to the Pathology Request Cover Letter, if specifically required by the pathology laboratory.

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### **3.1.4 HIPAA Authorization**

A copy of the site's HIPAA Authorization should be attached to the Pathology Request Cover Letter, if specifically required by the pathology laboratory. Keep a copy of the site's HIPAA Authorization and/or the original Authorization to Release Surgical Material in the participant's NLST site file.

### **3.1.5 Pathology Report**

A copy of the pathology report that describes the tissue(s) of interest should be attached to the Pathology Specimen Collection—Request Form. Keep the original pathology report in the participant's NLST site file.

### **3.1.6 Shipping Materials for Lending Pathology Laboratories**

NLST sites should include all appropriate shipping materials in the request packet to facilitate shipment of specimens from pathology laboratories. If a site should need shipping material or shipping labels, send a request by e-mail to the Remnant Tissue coordinator at [rmedina@acr-arrs.org](mailto:rmedina@acr-arrs.org). Please put "request for shipping material" in the subject line. The shipping materials to be included in the request packet are:

- Storage boxes for blocks (Fisher; dimensions 5" x 5" x 2").
- Multi-purpose insulated bio-shippers (Thermosafe Bio-Shippers; dimensions 14" x 10" x 14").
- Biohazard bags
- M3 carton sealing tape
- Styrofoam peanuts and/or bubble wrap.
- Cold Packs (to use for all shipments in climates with > 70°F temperature).
- Shipping labels to indicate: "Fragile—Handle With Care" and "Diagnostic Specimens – Not restricted, Packed in Compliance with IATA Packing Instruction 650"

### **3.2 Pathology Laboratory Non-Response Follow-Up for Specimen Request**

In the event that requested specimens are not received within three weeks of submitting the request, the NLST site coordinator will contact the local pathology department/laboratory and inquire if the laboratory received the request packet and if clarification or any further assistance is needed. If after two follow-up attempts, there is still no response, or if the pathology laboratory refuses to release any materials, the NLST site PI or designee will pursue negotiations with the pathology laboratory staff to gain access to these materials. The result of each follow-up effort will be documented on a hard copy Pathology Laboratory Non-Response Log: Request for Specimen(s) (**Appendix VI**). Non-response Logs should be stored in the participant's chart.

## **4. COLLECTING SPECIMENS AT STUDY CENTERS**

The lending pathology laboratory will receive the request packet and review the letter and accompanying form. If the pathology laboratory agrees to release the requested tissues, it will return the Pathology Specimen Collection—Request Form and the tissue to the NLST site in a pre-addressed, postage paid, shipping container. If the pathology laboratory is not willing to release the tissue, it should indicate the reason for refusal on the Pathology Specimen Collection—Request Form and fax or mail it back to the NLST site.

### **4.1 Receiving Specimens from Lending Pathology Laboratories**

Receiving specimen materials at the NLST site involves review of both the completed Pathology Specimen Collection—Request Form and the specimens. The NLST site will implement the following procedures for receipt of specimens:

1. Verify that a completed Request Form was returned. If the form is missing or incomplete, request that a completed form be provided. Note: if a request form is not returned, fill out a "Note to File" and store it in the participants chart.
2. Verify that each specimen corresponds to the tissue(s) requested. If there are any discrepancies, contact the pathology laboratory and complete a Discrepancy Notification Form (**Appendix VII**).
3. Inspect each specimen for damage. If a block is damaged, report the damage to the pathology department and request a replacement block if available. Extremely damaged blocks (i.e. melted, severely punctured, cut in half, severely smashed) should be returned to the pathology lab. If you are uncertain about the viability of a block, forward the specimen to UCLA Tissue Microarray (TMA) Core Facility and they will determine if the block can be processed.
4. The site coordinator should label each block with the NLST ID label supplied by ACRIN HQ and attach identical labels to the RT-Form in the row that corresponds to that particular block. The site coordinator should insure that any protected health information is de-identified prior to sending the specimens to the

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UCLA TMA Core Facility.

5. The NLST ID for each specimen is then entered into the NLST Remnant Tissue Tracking excel file.

#### 4.2 Labeling and Storing Specimens from Lending Pathology Labs

For tracking purposes, each specimen and its associated forms should be labeled with the NLST site number and case number. If a pathology laboratory identifier is visible on a block after application of the NLST ID label, supplied blank labels should be used as needed to mask the identifier. The trial-specific pathology specimen labels should be removed prior to eventual return to the lending pathology laboratories.

ACRIN will send pre-printed labels for all cases identified on the Remnant Tissue Case Selection List. If an NLST site identifies additional cases determined to be eligible for remnant tissue collection, the site coordinator should submit a 'Request for Case Specific Labels' form to ACRIN Headquarters. Indicate on the form that the labels will be used for NLST remnant tissue specimens. The 'Request for Case Specific Labels' form can be downloaded from the ACRIN Web site: <http://www.acrin.org> (Under Administration Menu, click on Administrative Resources, it is located under Documents).

The NLST ID number printed on each label will uniquely identify each tissue block of a participant. The ID numbers have the following format: (NNNN-NNNNN-NN)

NNNN: four-digit ACRIN site number

NNNNN: five-digit case number (case numbers range from 2 digits up to 5 digits)

NN: two-digit sequence number (starting at 01 and ending at 10)

If multiple blocks are obtained for a single specimen, each will have the same ACRIN site number and case number followed by an incremental sequence number. Follow the instructions below to label the tissue blocks and to prepare blocks for shipping.

1. Attach the NLST ID label to the side edge of the paraffin block cassette.
2. Attach the duplicate label to the corresponding row on the RT-form
3. Use blank labels to cover personal identifiers elsewhere on the cassette.
4. Place a copy of the pathology report in the biohazard bag form slot.
5. Place the cassette in the zip lock portion of the biohazard bag.
6. Place each bag in a 5" x 5" x 2" storage box. (Note: a box may fit 1-2 bagged specimens)
7. Store in ambient temperature with cool ventilation until the next scheduled shipping date to UCLA TMA Core Facility (see below).

#### 5. MAINTAINING AND SHIPPING SPECIMENS TO UCLA TMA CORE FACILITY

The pathology specimens are preserved in paraffin blocks. Prior to shipment, they should be stored in a cool, dark container and be protected from excessive light and temperature to prevent deterioration of the wax and embedded tissue.

Shipping methods should take seasonal temperatures into account, and include the use of extra insulated packaging and a cooling agent (cold packs), as needed. The standard shipping package for a specimen should include the biohazard bag, placed in a storage box, which is then placed inside a foam-insulated shipping box (bio-shipper).

Sites have pre-assigned shipment days (see below, Section 5.4). Shipment days are limited to Monday, Tuesday and Wednesday to avoid specimen receipt on Fridays, weekends, or holidays.

Specimens should be shipped on a weekly basis by overnight FedEx to the UCLA TMA Core Facility. The original RT Form (ACRIN website | Protocol 6654 Forms) and copies of the corresponding pathology report(s) should be included with the specimens. A copy of the pathology report should be faxed to ACRIN DM and the original retained in the NLST participant chart. On the day of shipment, the study coordinator will notify the UCLA TMA Core Facility via e-mail ([stze@mednet.ucla.edu](mailto:stze@mednet.ucla.edu)) or Fax (310-267-2940) of the upcoming shipment. Include the estimated date of arrival and the FedEx tracking number.

**NOTE:** The subject line of the email/FAX should include the following so that the UCLA TMA Core Facility staff can distinguish between blocks sent by ACRIN versus LSS sites:

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## ACRIN Specimen Block Shipment--Site [Name or ID].

Upon receipt of specimens, the UCLA TMA Core Facility will reconcile the materials and notify the NLST study coordinator of missing specimens, damaged specimens, or any concerns to be addressed.

### 5.1 Shipping Materials and Process

The appropriate shipping materials for NLST specimens are the following:

- Storage boxes for blocks (Fisher; dimensions 5" x 5" x 2")
- Multi-purpose insulated bio-shippers (Thermosafe Bio-Shippers; dimensions 14" x 10" x 14").
- Biohazard bags
- Shipping labels
- M3 carton sealing tape.
- Styrofoam peanuts and bubble wrap.
- Cold Packs (to use for all shipments in climates with > 70°F temperature).
- Shipping labels to indicate: "Fragile—Handle With Care" and "Diagnostic Specimens – Not restricted, Packed in Compliance with IATA Packing Instruction 650"

The packing process for shipments includes the following:

- Place a copy of the pathology report(s) for a single participant inside one biohazard bag, in the form slot, place the block(s) for that participant in the zip lock slot, then place the biohazard bag inside the white storage box (5" x 5" x 2").
- Pack the storage boxes containing the specimens in the shipping container box (14" x 10" x 14").
- Place packing materials such as Styrofoam peanuts and/or bubble wrap in and around the storage boxes to prevent them from shifting during transit.
- Place the RT Form(s) log inside a zip-lock bag and place the bag inside the insulated shipping container on top of the filler material.
- Close the lids and seal the shipping container with tape.
- Maintain a copy of the transmittal log at the site.

### 5.2 Labeling Shipping Containers

Label each shipping container with the FedEx shipping label to include the following:

1. The study coordinator return address
2. The UCLA TMA Core Facility address:  
Sheila Tze, Laboratory Manager  
David Geffen School of Medicine at UCLA  
UCLA TMA Core Facility  
Reed Neurological Research Center, Room 3243  
650 Charles E. Young Drive South.  
Los Angeles, California 90095  
  
Email: [stze@mednet.ucla.edu](mailto:stze@mednet.ucla.edu)  
Fax: 310-267-2940
3. Notice: Fragile --- Handle with Care
4. Notice: Diagnostic Specimens – Not restricted, Packed in Compliance with IATA Packing Instruction 650

Charge the shipping expenses to the 3rd Party ACRIN Account # 337439667 and remnant tissue reference number 6839.

### 5.3 Summary Shipping Task List

The following summarizes the tasks to complete by the site for a scheduled shipment:

- Prepare transmittal paperwork and retain copies at the NLST site.
- Send a notification e-mail | Fax to the UCLA TMA Core Facility listing the items being shipped, including: the number of storage boxes, FedEx tracking number, total number of blocks in the shipment, and the expected date of arrival. Please note "ACRIN Specimen Block Shipment--Site [Name or ID]." in the e-mail | Fax 'Subject' line.
- Pack the blocks according to instructions above.
- Label each shipping container with the FedEx shipping label as well as the labels indicating fragile contents

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and diagnostic specimens.

- Maintain a copy of the transmittal log at the site.

#### 5.4 **Scheduled Shipping Dates**

Refer to the table below for the scheduled shipping days for each site. Shipping to the UCLA TMA Core Facility should occur only on the assigned day, on a weekly basis. If a scheduled shipping day falls on a holiday or day of office closure, contact the UCLA TMA Core Facility to determine a make-up shipping day. Shipping should be limited to Monday, Tuesday, and Wednesday in order to minimize the chance of an over-weekend delivery delay.

Shipping days for NLST Site to the UCLA TMA Core Facility

<b>Monday</b>	<b>Tuesday</b>	<b>Wednesday</b>
4202	4206	4208
4214	4215	4218
4222	4227	4228
4240	4244	4248
4265	4274	4288
4473	4483	4487
4494	4496	4499
4217	4256	

#### 6. **RETURNING LOANED SPECIMENS**

Tissue blocks that do not need to be returned to the originating pathology laboratory will be maintained at the UCLA TMA Core Facility. Loaned blocks will be mailed to the NLST site for return shipment to the originating pathology laboratory.

The site should contact the UCLA TMA Core Facility to resolve any discrepancy or problem with return shipments. The NLST site is responsible for returning blocks within the timeframe specified by the lending pathology laboratory. If possible, loaned blocks can be batch-shipped to the lending pathology laboratories.

Transmittals for returns to pathology laboratories are generated by the NLST site. Materials are packaged as described for specimen shipments to the UCLA TMA Core Facility. NLST ID labels and blank masking labels should be removed prior to packaging for return.

**APPENDIX I**

**AUTHORIZATION COVER LETTER TEMPLATE**

**<< Letterhead of NLST Screening Center >>**

**National Lung Screening Trial (NLST)**

**<< Date >>**

**<< Participant Name >>**

**<< Participant Address >>**

Dear **<< Participant Title >> <<Participant Name >>**,

Thank you for your continued participation in the National Lung Screening Trial!

Our records show that since the time you started with the NLST, you have had a lung-related surgical procedure. We would like to obtain a small amount of the surgical material (also known as a pathology specimen) that was removed and preserved after your procedure. This will help future cancer research.

To allow us to obtain the material from the pathology lab, please sign the **<<Authorization Form(s)>>** included with this letter. We have enclosed two copies of the form. Please read, sign, and return one copy to us in the enclosed postage paid envelope. The other copy is for your records.

As you know, you have already given us consent for your involvement in NLST, but because of important HIPAA laws that are designed to protect the privacy of your medical information, we are asking for this additional authorization to obtain a portion of the pathology specimen from the pathology lab.

If you have any questions about this request or the NLST study, please call me or your NLST study coordinator, **<< study coordinator >>**, at **<< phone number>>**. Thank you very much for your help with our continuing research.

Sincerely,

**<< NLST Site PI >>**

**<< NLST Site PI Title >>**

**<< NLST Site >>**

Enclosures: Authorization Form (two copies)  
Self-addressed, stamped return envelope

**APPENDIX II**

**AUTHORIZATION TO RELEASE SURGICAL MATERIAL TEMPLATE**

**<< Letterhead of NLST Screening Center >>**

**National Lung Screening Trial (NLST)  
Authorization to Release Surgical Material & Related Health information  
that Identifies You for Research**

Your signature below gives permission to staff at **<< Pathology Lab Name >>** to release surgical material (also known as pathology specimen) and the related pathology report obtained during your diagnosis or treatment of lung cancer or related condition. The pathology specimen will be used for research in lung cancer detection, prevention and treatment by the ongoing National Lung Screening Trial (NLST), in which you are a participant.

This authorization is required by law to protect your health information. The pathology specimen and pathology report will be released to your local NLST screening center, identified at the top of this form. Any identifying information attached to the pathology specimen and pathology report such as your name, specimen ID or medical record number will be removed or blanked out before being sent to the NLST-ACRIN Central Laboratory located at the University of California at Los Angeles Tissue Array Core Facility. By signing this document, you authorize **<< Pathology Lab Name >>** to release your pathology specimen and pathology report for this research. Your local NLST screening center will hold your health information in confidence, will use it only for study purposes, and will not release it to anyone other than the study team unless required by law. Only the screening center and Central Laboratory staff involved with NLST research will have access to your pathology specimen and pathology report for this research.

Your medical treatment will not be affected in any way based on your decision to sign or not sign this Authorization.

You may change your mind and revoke this Authorization at any time, except to the extent that any actions have already been taken based on this Authorization. To revoke this Authorization, contact your local NLST screening center or write to **<< Pathology Lab Name >>**, **<< Pathology Lab Contact >>**, **<< Pathology Lab Address >>**. This authorization does not have an expiration date.

\_\_\_\_\_  
Signature of Participant or  
Participant's Personal Representative

\_\_\_\_\_  
Date Signed

\_\_\_\_\_  
Printed Name of Participant or  
Participant's Personal Representative

\_\_\_\_\_  
If Applicable, Description of  
Personal Representative's Authority

**APPENDIX III**

**PARTICIPANT NON-RESPONSE LOG: REQUEST FOR AUTHORIZATION**

<b>SECTION 1: PARTICIPANT DATA</b>				
NLST ACRIN Case #: _____				
Participant initials: _____				
Date of First Mailing: _____				
<b>SECTION II: CALL RECORD</b>				
Date of first mailing: _____				
Date of last contact: _____				
Day: _____ Date:        /        /2009 Time of call:        :        AM :        PM Initials: _____	<b>Outcome of Call</b> <input type="checkbox"/> No Answer <input type="checkbox"/> Busy <input type="checkbox"/> Call Back <input type="checkbox"/> Left Message <input type="checkbox"/> Already Sent <input type="checkbox"/> Refusal	<b>Reason for Refusal</b> <input type="checkbox"/> Too Busy <input type="checkbox"/> Not Interested <input type="checkbox"/> Call Back <input type="checkbox"/> Other, specify: _____	<b>Level of Refusal</b> <input type="checkbox"/> Mild <input type="checkbox"/> Firm <input type="checkbox"/> Hostile	<b>Comments:</b>
Day: _____ Date:        /        /2009 Time of call:        :        AM :        PM Initials: _____	<b>Outcome of Call</b> <input type="checkbox"/> No Answer <input type="checkbox"/> Busy <input type="checkbox"/> Call Back <input type="checkbox"/> Left Message <input type="checkbox"/> Already Sent <input type="checkbox"/> Refusal	<b>Reason for Refusal</b> <input type="checkbox"/> Too Busy <input type="checkbox"/> Not Interested <input type="checkbox"/> Call Back <input type="checkbox"/> Other, specify: _____	<b>Level of Refusal</b> <input type="checkbox"/> Mild <input type="checkbox"/> Firm <input type="checkbox"/> Hostile	<b>Comments:</b>
Day: _____ Date:        /        /2009 Time of call:        :        AM :        PM Initials: _____	<b>Outcome of Call</b> <input type="checkbox"/> No Answer <input type="checkbox"/> Busy <input type="checkbox"/> Call Back <input type="checkbox"/> Left Message <input type="checkbox"/> Already Sent <input type="checkbox"/> Refusal	<b>Reason for Refusal</b> <input type="checkbox"/> Too Busy <input type="checkbox"/> Not Interested <input type="checkbox"/> Call Back <input type="checkbox"/> Other, specify: _____	<b>Level of Refusal</b> <input type="checkbox"/> Mild <input type="checkbox"/> Firm <input type="checkbox"/> Hostile	<b>Comments:</b>
Day: _____ Date:        /        /2009 Time of call:        :        AM :        PM Initials: _____	<b>Outcome of Call</b> <input type="checkbox"/> No Answer <input type="checkbox"/> Busy <input type="checkbox"/> Call Back <input type="checkbox"/> Left Message <input type="checkbox"/> Already Sent <input type="checkbox"/> Refusal	<b>Reason for Refusal</b> <input type="checkbox"/> Too Busy <input type="checkbox"/> Not Interested <input type="checkbox"/> Call Back <input type="checkbox"/> Other, specify: _____	<b>Level of Refusal</b> <input type="checkbox"/> Mild <input type="checkbox"/> Firm <input type="checkbox"/> Hostile	<b>Comments:</b>
Day: _____ Date:        /        /2009 Time of call:        :        AM :        PM Initials: _____	<b>Outcome of Call</b> <input type="checkbox"/> No Answer <input type="checkbox"/> Busy <input type="checkbox"/> Call Back <input type="checkbox"/> Left Message <input type="checkbox"/> Already Sent <input type="checkbox"/> Refusal	<b>Reason for Refusal</b> <input type="checkbox"/> Too Busy <input type="checkbox"/> Not Interested <input type="checkbox"/> Call Back <input type="checkbox"/> Other, specify: _____	<b>Level of Refusal</b> <input type="checkbox"/> Mild <input type="checkbox"/> Firm <input type="checkbox"/> Hostile	<b>Comments:</b>

**APPENDIX IV**  
**PATHOLOGY REQUEST COVER LETTER TEMPLATE**

**<< Letterhead of NLST Screening Center >>**

**NATIONAL LUNG SCREENING TRIAL (NLST) PATHOLOGY TISSUE COLLECTION**

**<<Date>>**

Director, Pathology Department  
(Hospital Name)  
(Hospital Street Address)  
(Hospital City, State, Zip code)

Dear Director of Pathology Department,

We are writing to request your participation in a pathology specimen collection for the National Lung Screening Trial (NLST). **<< NLST Screening Center >>** is collaborating with the National Cancer Institute (NCI) on this trial. The purpose of the study is to determine the effects of imaging-based screening on lung cancer-related deaths. The lung cancers found by NLST screening are likely to represent earlier stages of disease. These specimens offer great potential to increase our understanding of lung cancer and its genetic and environmental causes as well as for improving lung cancer prevention and treatment efforts.

The specimens collected from the NLST will be used to construct tissue microarrays. Collected paraffin tissue blocks will have one slide (4 µm thick) cut for H&E staining, from which regions representative of a histology of interest for coring will be determined by a lung pathologist. The representative tissues of interest include:

- The predominant and secondary histologies or grades of the primary lung cancer
- Normal (non-tumor) lung, including the distal airspaces, proximal bronchus, and peripheral bronchiolar tissues
- Metastases in lymph nodes or resected metastases from other organ sites.

If multiple blocks are provided for a single histology, cores may be distributed among the blocks for improved capture of histologic and molecular heterogeneity.

The NLST participant listed on the attached Request Form has given signed consent and authorization to collect these lung cancer-related pathologies. These forms as well as a copy of the pathology report pertinent to this pathology material are provided.

The Pathology Request Form specifies the material we are requesting. For tumors, we are requesting the most representative specimen(s) of the tumor (include all representative histologies or grades) as well as tumor-free margin. Blocks that include non-tumor involved central bronchus, peripheral bronchiolar tissue, and lung parenchyma are also requested. A minimum 3-month loan period will be required by the Pathology Core to process this specimen block.

Ship the specimen(s) and copy of the Request Form using the enclosed self-addressed, postage paid shipping materials. Please advise us of any additional costs associated with this request for preserved tissue.

Thank you for your assistance with this research. If you have any questions, please call me or our study Coordinator: **<<Site Study Coordinator>>** at **<<Phone Number>>**.

Sincerely,

**<<NLST Site PI>>**

Enclosures: Pathology Request Form  
Pathology report  
Informed consent  
Authorization Form for release of pathology specimens (if required)

Participant Name: \_\_\_\_\_  
Date of Birth: \_\_\_\_\_  
Medical Record #: \_\_\_\_\_

The NLST participant listed above reported resection of a lung cancer at your institution. We are requesting that you provide us with **buffered formalin-fixed paraffin blocks** of the tissue types listed below. For each block, please record the date of procedure, explicit block identification, and provide any additional comments as appropriate.

If no specimens will be sent, please indicate the reason below and fax to << Site FAX >>.

[ ] NO specimens shipped Reason \_\_\_\_\_

Procedure Date	Tissue Type	Unique Block Identification	Comments about Block
	Primary Lung Tumor 1 <sup>st</sup> histology and grade		
	Primary Lung Tumor 2 <sup>nd</sup> histology or grade		
	Normal Lung Tissue		
	Metastatic Lymph Nodes		
	Resected Metastases		
	Non-tumor involved proximal bronchus		
	Non-tumor involved distal bronchioles		

- How soon does material need to be returned to your facility (check box)?  Permanent retention is permitted.  Return in \_\_\_\_ months (3 months minimum required).
- Please ship this form and the requested specimen(s) using the enclosed pre-paid packaging. OR, if no specimen can be sent, please indicate reason above and fax this form to:  
 <<NLST Site Fax #, Attn: << NLST Site Coordinator>>>.  
 <<Name of NLST Site>>  
 <<NLST Site Street Address>>  
 <<City, State, Zip code>>

This report contains data protected by HIPAA. Distribute only to authorized staff, and store and dispose in a proper manner.

**APPENDIX VI**  
**PATHOLOGY LABORATORY NON-RESPONSE LOG: REQUEST FOR SPECIMEN(S)**

<p>Instructions: The Non-response Log should be used to document effort to obtain remnant tissue from a pathology lab. Guidelines for follow-up effort are included in the Remnant Tissue MOP section 3.2.</p>				
<b>Section I: Participant Data</b>		<b>Section II</b>		
ACRIN NLST Inst #		Pathology Lab Name		
ACRIN NLST Case #		Pathology Lab Address		
Participant Initials:		Pathology Lab Address		
		Pathology Lab Address		
		Contact Person at Lab		
		Phone		
		Fax		
<b>Section III: Call Record</b>				
Date of first mailing: _____				
Date of last contact: _____				
Day: _____ Date: ____/____/2009 Time of call: ____:____ AM ____:____ PM Initials:	<b>Outcome of Call</b> <input type="checkbox"/> No Answer <input type="checkbox"/> Busy <input type="checkbox"/> Call Back <input type="checkbox"/> Left Message <input type="checkbox"/> Already Sent <input type="checkbox"/> Refusal	<b>Reason for Refusal</b> <input type="checkbox"/> Too Busy <input type="checkbox"/> Not Interested <input type="checkbox"/> Call Back <input type="checkbox"/> Other, specify:	<b>Level of Refusal</b> <input type="checkbox"/> Mild <input type="checkbox"/> Firm <input type="checkbox"/> Hostile	<b>Comments:</b>
Day: _____ Date: ____/____/2009 Time of call: ____:____ AM ____:____ PM Initials:	<b>Outcome of Call</b> <input type="checkbox"/> No Answer <input type="checkbox"/> Busy <input type="checkbox"/> Call Back <input type="checkbox"/> Left Message <input type="checkbox"/> Already Sent <input type="checkbox"/> Refusal	<b>Reason for Refusal</b> <input type="checkbox"/> Too Busy <input type="checkbox"/> Not Interested <input type="checkbox"/> Call Back <input type="checkbox"/> Other, specify:	<b>Level of Refusal</b> <input type="checkbox"/> Mild <input type="checkbox"/> Firm <input type="checkbox"/> Hostile	<b>Comments:</b>
Day: _____ Date: ____/____/2009 Time of call: ____:____ AM ____:____ PM Initials:	<b>Outcome of Call</b> <input type="checkbox"/> No Answer <input type="checkbox"/> Busy <input type="checkbox"/> Call Back <input type="checkbox"/> Left Message <input type="checkbox"/> Already Sent <input type="checkbox"/> Refusal	<b>Reason for Refusal</b> <input type="checkbox"/> Too Busy <input type="checkbox"/> Not Interested <input type="checkbox"/> Call Back <input type="checkbox"/> Other, specify:	<b>Level of Refusal</b> <input type="checkbox"/> Mild <input type="checkbox"/> Firm <input type="checkbox"/> Hostile	<b>Comments:</b>
Day: _____ Date: ____/____/2009 Time of call: ____:____ AM ____:____ PM Initials:	<b>Outcome of Call</b> <input type="checkbox"/> No Answer <input type="checkbox"/> Busy <input type="checkbox"/> Call Back <input type="checkbox"/> Left Message <input type="checkbox"/> Already Sent <input type="checkbox"/> Refusal	<b>Reason for Refusal</b> <input type="checkbox"/> Too Busy <input type="checkbox"/> Not Interested <input type="checkbox"/> Call Back <input type="checkbox"/> Other, specify:	<b>Level of Refusal</b> <input type="checkbox"/> Mild <input type="checkbox"/> Firm <input type="checkbox"/> Hostile	<b>Comments:</b>

**APPENDIX VII**

**NATIONAL LUNG SCREENING TRIAL (NLST) – PATHOLOGY SPECIMEN COLLECTION  
DISCREPANCY NOTIFICATION**

**To:** \_\_\_\_\_

**FROM:** \_\_\_\_\_

**DATE:** \_\_\_\_\_

**SUBJECT: Problem with NLST specimen shipment dated:** \_\_\_\_\_

**SPECIMEN ID:** \_\_\_\_\_

**PROBLEM DESCRIPTION:** \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

**PROBLEM RESOLUTION:** \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

**DATE OF RESOLUTION:** \_\_\_\_\_