



Biospecimen Collection on CALGB Trials

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For CALGB Participants Only

Objectives

- Review the CALGB biospecimen repositories (policies and procedures, audit process, inventory management, etc.)
- Review some important aspects of specimen collection and how correlative studies can impact future trials
- Present an overview of the new CALGB Specimen Tracking System and the timeline for release
- Summarize the improvements that we hope to have in place by the end of 2008.

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CALGB Specimen Repositories

- The Pathology Coordinating Office (PCO)
 - The PCO resides at The Ohio State University and is the repository for biospecimens associated with solid tumors studies as well as lymphoma studies. The PCO receives all types of biospecimens such as: tissue (FFPE and frozen), slides for central morphology review, serum, plasma and whole blood for PGx.
- The Leukemia Tissue Bank (LTB)
 - The LTB also resides at The Ohio State University and stores specimens from patients with acute or chronic leukemia, myelodysplastic syndrome (MDS) and multiple myeloma who are entered on a CALGB protocol. The LTB primarily receives blood and bone marrow specimens.

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PCO Inventory

CALGB Biospecimens Collected 1/1/2003 – 2/29/2008 (by Committee)

Committee	Cases	Blocks	Slides	Blood	Plasma	Serum	Urine
Breast	9,509	3,335	10,704	16,313	195	1,378	0
CCHO	71	1	569	252	0	0	0
GI	2,397	2,464	26,849	1,718	5,320	2,549	2,693
GU	2,106	731	5,680	23,792	5,476	1,041	5,160
Lymphoma	724	300	5,221	367	0	0	0
Melanoma	367	988	2,598	0	0	0	0
PET	4,438	0	0	9,136	0	0	0
Respiratory	758	290	3,985	1,083	6	1,153	0
Surgery	611	110	6,880	0	0	0	0
Transplant	24	4	214	0	0	0	0
Totals	21,005	8,223	62,700	52,661	10,997	6,121	7,853

CALGB Specimen Repositories

- The Lung Cancer Tissue Bank (LCTB)
 - The LCTB is located at the Brigham And Women’s Hospital. This repository is governed by one CALGB protocol (CALGB 140202). The purpose of the LCTB is to collect, catalog and store frozen samples of lung carcinoma and when possible, portions of involved lymph nodes and adjacent uninvolved lung tissue obtained from previously untreated patients. In addition to tissue specimens, blood samples are also collected pre- and post-resection from the patients to provide a source of quality DNA, RNA and protein for molecular studies.

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LCTB 2004-present

Specimens received at the LCTB

Pre-op blood received	692	98%
Pre-op blood received overnight	655	95%
Post-op blood received	534	75%
Post-op blood received overnight	493	92%
Post-op blood w/in window (4-12 weeks post-op)	374	70%
Frozen tissue received	686	97%
Frozen tissue received overnight	653	95%
Formalin-fixed Paraffin-embedded received	590	83%

Histologic classification of 636 eligible cases for which pathologic diagnosis has been reported to date is representative of the spectrum of resected early stage primary lung cancer in the US.

Histology of eligible cases

Adenocarcinoma	318	50%
Squamous cell carcinoma	234	37%
Large cell carcinoma	25	3.9%
Undifferentiated non-small cell carcinoma	16	2.5%
Bronchioloalveolar carcinoma	15	2.4%
Adenosquamous carcinoma	9	1.4%
Small cell lung carcinoma	8	1.3%
Carcinoid tumor	4	0.6%
Other	4	0.6%
Large cell neuroendocrine tumor	3	0.5%

Policies and Procedures

- The CALGB repositories store specimens only from patients who are pre-registered or registered on a study coordinated by CALGB or another cooperative group.
- Specimens are not released from the repository to investigators until the appropriate paperwork is in place and patient consent is verified by the CALGB statistician assigned to the study.
- All specimens managed by the repositories are tracked by a database system.
- For paraffin block specimens that have been submitted to the Pathology Coordinating Office (PCO), the appropriate quality control slides will be prepared and remain on file and will be available to the submitting institution for any medical-legal need.

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Policies and Procedures

- A unique specimen bank identification number is given to each specimen. Specimens must be stored and distributed with this number only.
- Unless indicated in the protocol, as necessary to determine eligibility or randomization, results from correlative science studies may not be provided to the patient or physician.
- The repository director is responsible for ensuring that the appropriate quality control and quality assurance procedures are in place for specimen handling, processing, storage and distribution.
- The repository will undergo periodic audits to ensure compliance with CALGB and NCI policies. Oversight for the audits of the repositories will be a function of the CALGB Biospecimen and Correlative Science Advisory Committee (BCSAC).

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BCSAC

- M. Bertagnolli
- P. Febbo
- M. Ellis
- B. Kratzke
- J. Byrd
- R. Bueno
- H. McLeod
- A. Thor
- R. Cheney
- E. Hsi
- D. Collyar
- P. Friedman
- K. Karas
- M. Kelly
- D. Sawyer
- K. Owzar
- K. Johnson
- Repository and Lab directors

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OBBR Guidance Document

- The NCI established the Office of Biorepositories and Biospecimen Research (OBBR) in 2005 to guide, coordinate, and develop the NCI's biospecimen resources and capabilities. The OBBR's mission is to ensure that human specimens available for cancer research are of the highest quality.
- Early last year the OBBR sent out a draft guidance document entitled "Best Practices For Biospecimen Resources" and solicited feedback which we provided.
- The guidance document was issued in June 2007.

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Repository Audits

- The BCSAC used the NCI OBBR Biorepository Best Practices Guidelines as a guide and performed an internal audit of the 3 CALGB repositories. Physical site visits were conducted at the PCO and the LTB in November of 2007 and at the LCTB in January of 2008.
- Drs. Paula Friedman and Monica Bertagnolli (Chair of BCSAC) performed the audits. In addition, the repository directors served as reviewers for each other's facility.
- All 3 repositories were found to be in compliance with the guidelines.

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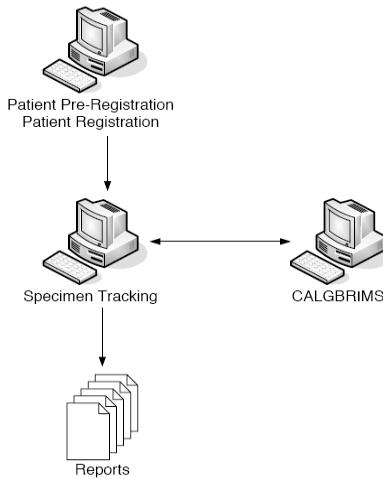
CALGB RIMS

- The CALGBRIMS database was designed by the PCO Director, coordinators, pathology research associates and the PCO Informatics group.
- The database was written/coded by Jasmine Ramaradjou who is the manager of PCO Informatics. The database is caBIG compliant and provides great functionality that fits the PCO and LTB specific operational needs.
- The database is designed to use barcode procedures for efficient logging, banking and retrieval of biospecimens.
- The CALGBRIMS database is the biospecimen inventory system for the PCO and LTB and is part of the overall CALGB database system that is managed by the CALGB Information Systems group. Web services are being implemented to provide the needed real time communication between OSU and Duke.

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Data Flow Schematic



Strategic Planning Retreat

November 29th, 2007

- Session I - Trial Designs to Meet Correlative Science Goals (Bertagnolli, Febbo, Hawk)
- Session II - Biology Driven vs. Disease Driven (Janne and Hurwitz)
- Session III - Which technologies? Which laboratories? (McLeod and Perou)
- Group Discussion/Recommendations

Recommendations

- CALGB should conduct biomarker validation studies to obtain level I evidence whenever possible. These studies are required to change patient care and are within the primary mission of CALGB
- CALGB should continue to support biomarker development studies, companion studies embedded in treatment protocols, because this endeavor can have significant added scientific value.
 - For example: a negative clinical trial result complemented by significant, positive correlative science result in phase III adjuvant trials.
 - Investigators should design biomarker development studies that if successful will lead to definitive biomarker validation studies (analogous to planning for phase II-III progression in drug development).

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Recommendations

- CALGB investigators should develop a minimum standard set of markers to be tested in specific pathways across disease types. This will help to standardize between correlative science investigators in different disease groups.
- CALGB should develop sample collection and assay SOPs for common processes as well as assays (e.g., HER-2, EGFR, etc.) that are being done in multiple studies across disease sites.
- Core/reference laboratories (CLIA/CAP certified) should be utilized when a biomarker reaches the validation phase. Core/ reference laboratories (perhaps at least CLIA certified) should be strongly encouraged for development studies, or for biomarkers used by multiple studies and/or across multiple disease sites (e.g., HER-2 and EGFR).

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Specimens and CS Research

- Specimen collection and processing is key to good CS studies. This is critical to the success of CALGB!
- Many specimens need to be processed at the site. This adds variability but it may be critical for the sample to be processed within 24 hours for the marker analysis.
- If it is not critical for a sample to be processed immediately then we prefer to have the specimen processed at the repository.
- We are in the process of developing standard SOPs (BCSAC)

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Specimen Collection Kits

- CALGB 90203 - neoadjuvant PCa
 - Collection of frozen biopsies
- CALGB 40503 - metastatic BCa
 - Collection of CTCs and proteomic samples
- CALGB 40601/40603 - neoadjuvant BCa
 - Collection of frozen biopsies and CTCs (40601)
- CALGB 30506 - early stage NSCLC
 - Collection of frozen biopsies

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Good Correlative Research Informs New Trials

- Correlative research done on retrospective specimens often leads to ideas for new marker driven studies
 - IgVh and FLT3 mutations - CALGB 10501 and CALGB 10603
 - Cox-2 analysis - CALGB 30801
 - K-RAS - amendment to CALGB 80405
 - Lung Metagene Predictor - CALGB 30506

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Development of a New Specimen Tracking System

- Specimen tracking is critical to the success of our CS studies. We need to be able to:
 - Monitor specimen submissions in real-time
 - Contact sites when a required sample is missing
 - Produce accurate/up-to-date audit reports
 - Record data electronically - no more paper forms!
 - Decrease the burden on the sites and the repositories

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STS Steering Committee

- Assembled a team to develop the Functional Requirements for the new system and oversee the development process
 - Central Office: P. Friedman, M. Kelly
 - IS: D. Ens, B. Martin, A. Shah, K. Johnson
 - Stats/DCs: G. Broadwater, E. Leung
 - Repositories: D. Bucci, S. Jewell, B. Richards, J. Ramaradjou, C. Vetanovetz, D. Rohrer
 - CRAs: H. Weiner, J. Cuevo, M. Dierker

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Functional Requirements Summary

- System will be user-friendly
- System will be web-based and accessible to all sites that register patients on CALGB trials
- System will be pre-loaded with the information about the specimen collection events
- Users will be able to search and retrieve data about patients registered and/or specimens logged
- System will exchange data with both the registration system and the inventory management systems at the repositories.

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This is the Home screen. It shows tasks specific to a CRA.

Select	From	Date	Subject
<input type="radio"/>	David Jones, PCO	Jun 11, 2008	Specimen Damaged
<input type="radio"/>	Alice Brown, LTB	Jun 11, 2008	Shipment Received

Links to search for Patients, Specimens, or Shipments. When you select one of these items, there are several search criteria. For example, you can search by the Patient's CALGB ID or by their Hospital ID (MRN).

The Home screen also has an Inbox. Here it shows 2 notes from 2 different repository labs.

You click anywhere on the row to go to the Note screen.

After you have read the note you can remove it from the Inbox.

When logging a specimen, one can begin by searching for a patient record.

Patient Initials	CALGB ID™	Study ID	MRN
A, B C	112017	8461, 9665, 9862, 10403	HOSPITAL-123

In the "Search" panel, select "Patients", enter the patient's ID and click on the magnifying glass to see search results.

Click on the patient's initials to go to their Specimen Checklist.

There are instructions at the top of the screen.

The instructions are a helpful guide at first. But they can be turned off by clicking on the Hide Instructions icon.

The Specimen Checklist is the heart of the program.

It shows the specimens that should be collected for all studies that the patient is enrolled on (and has consented to).

Across the top of the screen are the time-periods, such as Pre-Treatment, During Treatment, Follow-up, Remission, and Relapse.

Within each time-period you can see the collection events.

To log a specimen you simply click on the checkbox, add the date, and click on Add to Shipments.

Collected	Study	Specimens Expected	Collection Date	Status
<input type="checkbox"/>	8461	20 ml Pheripheral Blood 1 Green Top Tube		
<input type="checkbox"/>	8461	3 ml Bone Marrow Aspirate 1 Syringe		
<input type="checkbox"/>	9862	20 ml Pheripheral Blood 1 Green Top Tube		
<input type="checkbox"/>	9862	5 ml Bone Marrow Aspirate 2 Green Top Tubes		
<input type="checkbox"/>	10403	3 Unstained Bone Marrow Smears		
<input type="checkbox"/>	10403	3 Unstained Blood Smears		
<input type="checkbox"/>	10403	1 H & E Stained Biopsy Slide		
<input type="checkbox"/>	10403	4 Unstained Sloppy Sections		
<input type="checkbox"/>	9665	2 Buccal Swab(s) Cervical Screw Cap Tube(s)		
<input type="checkbox"/>	9665	10 ml Pheripheral Blood 1 Green Top Tube		
<input type="checkbox"/>	9665	5 ml Bone Marrow Aspirate 1 Green Top Tube		

If a note needs to be attached or if additional information is required, you will click on the Note icon to go to that screen.

Here we have turned off the instructions.

Notes for Specimens

Specimen ID: 300223

Specimen Description: 5 ml Bone Marrow Aspirate
2 Green Top Tubes

For Study ID: 9862

For Timepoint: Pre-treatment

For Patient: 112017 A, B, C

Status: In Shipment

Note Type: Incomplete Submission

Note: For 9862 Pre-Treatment, 2 tubes of bone marrow are required. Only 1 could be obtained.

From	Date	Note Type	Note
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Additional Details

Pathology Numbers:

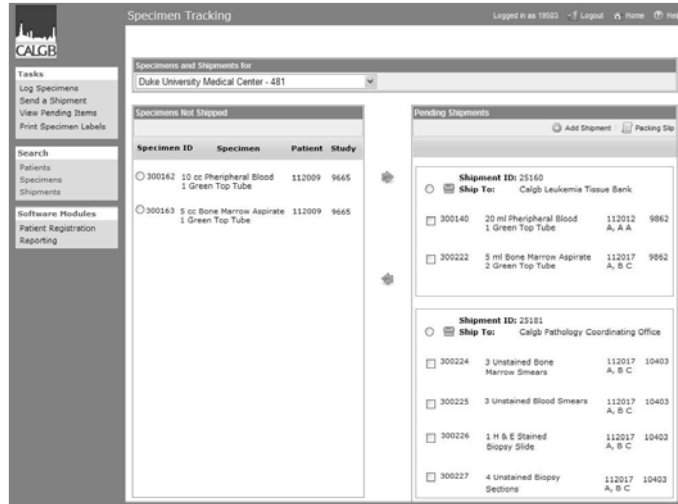
The Notes screen can be used to attach a note to a specimen and send it to the repository lab.

The repository lab can respond.

This correspondence between collecting site and repository lab will show in the Note History table.

The Additional Details section will be used for the fields that were previously found on paper forms.

The Pending Shipments screen shows the contents of all shipments not sent yet.

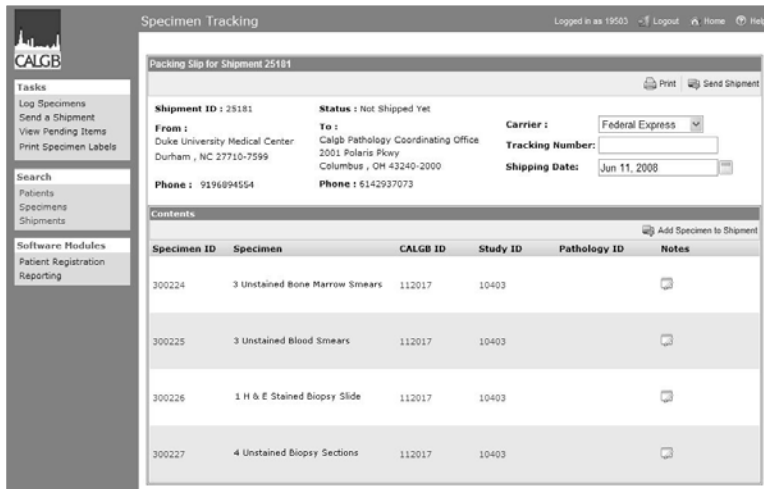


The destination is pre-determined by the protocol.

However, this screen lets you add specimens to a box. Also, one can move specimens to a different box if necessary. This is helpful if there are 2 boxes going to the same destination and 1 box is full. You can move specimens from the full box to the other one.

After viewing the Pending Shipments screen, you can select a shipment and click on the Packing Slip icon to see details for that particular shipment.

The Packing Slip shows details for a shipment.



The Packing Slip shows details for a shipment.

You will need to print the Packing Slip and include it in the shipment.

Click on the Send Shipment icon to alert the Repository Lab that the shipment is on its way.

At the Repository Lab, the person receiving the shipment will use the Packing Slip to pull up the record on their computer and acknowledge receipt of the shipment.

Timeline

- Project initiation - Jan 2007
- Functional Requirements - July 2007
- Internal Testing - July 2008
- Beta Site Testing - August 2008
- Tentative Launch - Nov/Dec 2008

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Beta Testing Sites

- OSU
- Wake Forest
- Wash U
- West Penn
- Roswell Park
- NorthShore
- U of Chicago
- Duke
- Dana Farber
- MSKCC
- Kaiser
- UCSF

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Summary of the Biospecimen and CS Initiatives

- Repository audits
- CS Retreat - to discuss improvements in specimen collection and correlative research opportunities
- SOPs for sample collection
- Specimen collection kits
- Standardized consent questions in protocols (new GBC document is in development)
- CALGBRIMS
- New Specimen Tracking System

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Resources

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