NLST-ACRIN Biomarker Repository

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Abstract

The National Lung Cancer Screening Trial (NLST) is a multicenter randomized trial sponsored by NCI to study whether screening for lung cancer with low dose helical computed tomography (LDCT) would reduce lung cancer specific mortality compared to screening with standard chest X-ray (CXR). From September 2002 to April 2004, the NLST enrolled about 54,000 high risk participants from 33 sites across the United States.

An important component of the NLST is the Lung Cancer Biospecimen Research Opportunity which was conducted by the American College of Radiology Imaging Network (ACRIN) - one of the two funded groups in the NLST. Blood, urine and sputum samples collected at each of the 3 NLST screening time points were designed to serve as a unique resource for the early detection and molecular characterization of lung cancer.

The collected specimens were mailed and archived in the University of Colorado Health Sciences Center – SPORE Laboratory, whereas the associated clinical and outcome data were collected and warehoused in the ACRIN Data Management center.

In November 2010, the ACRIN announced the availability of this repository for research application.

Objectives

Lung cancer is the leading cause of cancer-related deaths in the Western world, accounting for more deaths than those caused by prostate, breast, and colorectal cancer combined. It is estimated that in the United States in 2009, there were 219,440 new cases of lung cancer diagnosed, and 159,390 deaths were attributable to lung cancer. Lung cancer is difficult to detect in its early stages. In most cases, tumors are detected at advanced stages and the overall 5 year survival rate is roughly 16 percent. In contrast, the 5 year survival of individuals with resected stage 1A disease approaches 70%.

Beyond the objective of NLST to compare mortality rates between CT-screened and CXR-screened individuals, biospecimen collection was a central goal. By coupling biospecimen collection with imaging-based screening, the NLST-ACRIN Biorepository is relatively enriched for early clinical stage lung cancers and associated remote media that were collected longitudinally. In addition, resected tissue collection includes tissues that reflect field injury, premalignant lesions, carcinoma *in situ* and overtly invasive lung cancer. Core programmatic objectives of the NLST-ACRIN investigators are the elucidation of molecular biomarkers of lung cancer--genetic, epigenetic, proteomic, metabolomic, stem cell--that can inform such core questions as which biomarkers, or panels of biomarkers can:

- Predict lung cancer
- Detect early lung cancer
- Sub-classify lung cancers into biological phenotypes that will inform more effective treatments across the horizon of management.

Specimens Collection

Biospecimens collected on participants at each of the three screening time points included:

- Peripheral blood separated on site into plasma and buffy coat
- One urine sample, unprocessed
- Sputum (processed into cell pellet and supernatant)

Specimens collected across the trial

Specimen Type	Samples	Number Participants	Participants with ≥ 1 sample (N)	Participants with ≥ 1 sample (%)
Plasma	108,666	10,218	10, 133	99.17%
Buffy coat	108, 891	10,218	10,132	99.16%
Urine	55,332	10,247	10,168	99.23%
Sputum cell pellet	39,544	8,336	8,173	99.04%

Specimens collected at each screening time point

Specimen Type	T0		T1		T2		Total	
	Samples	Subjects	Samples	Subjects	Samples	Subjects	Samples	Subjects
Plasma	38,454	9,683	34,729	8,759	32,301	8,181	105,484	10,133
Buffy coat	38,517	9,681	34,781	8,752	32,405	8,181	105,704	10,132
Urine	19,481	9,735	17,630	8,816	16,625	8,334	53,736	10,168
Sputum cell pellet	15,548	6,927	12,188	5,965	9,747	5,036	37,483	8,173

Paraffin embedded tissues of resected lung cancers have also been collected retrospectively for the creation of tissue microarrays. When possible, the tissues procured for TMA construction included:
- The predominant and secondary histologies (or grades) of the primary lung cancer
- Normal (non-tumor) lung, to include distal airspaces, the bronchus proximal to the lesion, and peripheral bronchiolar tissues
- Resected metastases in lymph nodes or other organ sites

Progress to date
- 540 blocks received at UCLA (204 cases)
- 532 slides sectioned for Colorado pathologist annotation
- 169 cases arrayed thus far

Two Committees

Research Evaluation Panel (REP)

- Identify the science best served by use of the specimens and correlative data
- Oversee and develop procedures for strategic marketing of resource
- Develop guidelines and application forms for requesting MATERIAL
- Develop guidelines for peer-review of proposals

Member	Affiliation
Steven M. Dubinett, MD | Chair	UCLA Jonsson Comprehensive Cancer Center
Pierre P. Massion, MD | Co-chair	Vanderbilt Ingram Cancer Center
Neil E. Caporaso, PhD	Division of Cancer Epidemiology and Genetics | NCI
Edward F. Patz, MD	Duke University Medical Center
Fred Hirsch, MD PhD	University of Colorado, Denver, School of Medicine
John D. Minna, MD	Graduate School of Biomedical Sciences at UT Southwestern
Denise R. Aberle, MD	UCLA Jonsson Comprehensive Cancer Center
Constantine Gatsonis, PhD	ACRIN Biostatistics and Data Management Centers
Charles Apgar	ACRIN Headquarters | Director ACRIN Operations
Rosa Medina	ACRIN Headquarters | Project Manager

Two Committees (cont.)

Tissue Bank and Biomarker Oversight Committee (TBBmOC)
- Oversee & develop policies and procedures that govern the collection, archiving, quality assurance of the NLST-ACRIN Biorepository.
- Appraise the NLST ACRIN Biorepository at University of Colorado
- Members with expertise in management and appraisal of specimen biorepository

Member	Affiliation
William Grizzle, MD Chair	University of Alabama at Birmingham
Wilbur Franklin, MD	Pathology, University of Colorado Cancer Center
Neil e. Caporaso, PhD	Division of Cancer Epidemiology and Genetics, NCI
Denise R. Aberle, MD	David Geffen School of Medicine at UCLA | JCCC
Fenghai Duan, PhD	ACRIN Biostatistics and Data Management Centers
Rosa Medina	ACRIN Headquarters | Project Manager

Quality Assessment

- During January 26-28, 2009, ACRIN conducted a site audit to ensure that specimens were received, processed and archived appropriately and to assess the quality of the archived specimens.
- The ACRIN Biostatistical Center at Brown University selected 2,400 random samples - 600 per type (Sputum, Urine, Plasma, Buffy Coat) - to be assessed with regards to their locations, volume, discoloration, DNA/RNA concentration, and RNA quality.

Quality Assessment of NLST-ACRIN Biorepository

	Urine	Sputum (cell pellet)	Plasma	Buffy coat
Location	99.6%	99.8%	99.5%	100%
Sufficient Volume	98.7%	91.7%	77.9%	98.7%
Adequate Color	98.3%	(NA)	91.1%	(NA)

Buffy coat DNA/RNA:
DNA concentration: mean 53.1 ng/UL
RNA integrity number: mean 3.1

Summary

- A unique resource of specimens for the early detection and molecular characterization of early lung cancer.
- Primarily for validation studies once appropriate biomarker(s) have been identified and translational pilot projects have provided evidence of the potential of biomarker(s) in clinical medicine.
- http://www.acrin.org for the details of the application process

References

- Patz EF, Caporaso NE, Dubinett SM, Massion PP, Hirsch FR, Minna JD, Gatsonis C, Duan F, Adams A, Apgar C, Medina RM, Aberle DR. NLST ACRIN Biomarker Repository Originating from the Contemporary Screening for the Detection of Lung Cancer Trial (NLST, ACRIN 6654): Design, Intent, and Availability of Specimens for Validation of Lung Cancer Biomarkers, *Journal of Thoracic Oncology*. July 2010

- Announcement of NLST-ACRIN Biospecimen Research Opportunity (http://www.acrin.org)

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