AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 4704

Detection of Early Lung Cancer Among Military Personnel Study 2 (DECAMP-2): Screening of Patients with Early Stage Lung Cancer or at High Risk for Developing Lung Cancer

Study Chair
Avrum Spira, MD, MSc
Boston University School of Medicine
Division of Computational Medicine
72 East Concord St. E633
Boston, MA 02118
Phone: 617-414-6980
Fax: 617-414-6999
Email: aspira@bu.edu

Study Chair
Mitchell Schnall, MD, PhD
University of Pennsylvania
Department of Radiology
MRI 1 Founders Pavilion
3400 Spruce Street
Philadelphia, PA 19104
Phone: 215-662-7238
Fax: 215-662-3013
Email: mitchell.schnall@uphs.upenn.edu

Co-Chair
Steven Dubinett, MD
University of California at Los Angeles
Department of Medicine
UCLA Medical Center, 37-131 CHS
10833 Le Conte Avenue
Los Angeles, CA 90095
Phone:310-794-6566
Fax: 301-2672829
Email: sdubinett@mednet.ucla.edu

Co-Chair
Daniel G. Remick, MD
Boston University
Department of Medicine
670 Albany Street, Room 407
Boston, MA 02118
Phone: 617-414-7043
Fax: 617-414-6999
Email: *remickd@bu.edu*

Study Chair
Ignacio I. Wistuba, MD
MD Anderson Cancer Center
Department of Pathology
1515 Holcombe Blvd, Unit 0085
Houston, TX 77030
Phone: 713-563-9184
Fax: 713-792-1220
Email: iiwistuba@mdanderson.org

Study Chair
Marc Lenburg, PhD
Boston University
Department of Medicine
670 Albany Street, Room E-613B
Boston, MA 02118
Phone: 617-414-1375
Fax: Insert Fax Number
Email: mlenburg@bu.edu

Study Chair
Pierre P. Massion, MD
Vanderbilt University
2200 Pierce
Preston Research Building, Room 640
Nashville, TN 37232
Phone: 615-936-2256
Fax: 615-936-1790
Email: pierre.massion@vanderbilt.edu

Study Statistician
David Elashoff, PhD
University of California at Los Angeles
David Geffen School of Medicine
Room 21-254C CHS, Dept of Biostatistics
Los Angeles, CA 90095
Phone: 310-794-7835
Fax: 310-267-2113
Email: delashoff@mednet.ucla.edu

Study Statistician
Constantine Gatsonis, PhD
Brown University
Center for Statistical Sciences
Box G-S121-7
121 South Main Street, 7th FloorPhone:
Providence, RI 02912
Phone: 401-863-9183
Fax: 401-863-9182
Email: gatsonis@stat.brown.edu

Study Statistician
Fenghai Duan, PhD
Brown University
Center for Statistical Sciences
Box G-S121-7
121 South Main Street, 7th Floor
Providence, RI 02912
Phone: 401-863-2175
Fax: 401-863-9182
Email: fduan@stat.brown.edu

Original Date: May 1, 2012
Version Date: August 6, 2014
Activation Date: September 10, 2013
Includes Amendments 1-3
Administrative Update: September 16, 2014

Limited Site Participation

The Detection of Early lung Cancer Among Military Personnel (DECAMP) consortium is a multidisciplinary and translational research program that includes 7 Veterans Administration Hospitals (VAH), the 4 designated Military Treatment Facilities (MTF) and two academic hospitals as clinical study sites, several molecular biomarker laboratories, along with Biostatics, Bioinformatics, Pathology and Biorepository cores.

The clinical sites will include: Naval Medical Center, Portsmouth, VA; Walter Reed National Military, MD; Naval Medical Center San Diego, CA; San Antonio Military Center, TX; Veterans Administration Boston Healthcare System, MA; Dallas Veterans Administration Medical Center, TX; Denver Veterans Administration Medical Center, CO; Greater LA Veterans Administration Healthcare System, CA; Veterans Administration Tennessee Valley Healthcare System, TN; Hospital of the University of Pennsylvania, PA; Philadelphia Veterans Administration Medical Center, PA; Veterans Administration Pittsburgh Healthcare System, PA; and Roswell Park Cancer Institute, Buffalo, NY.

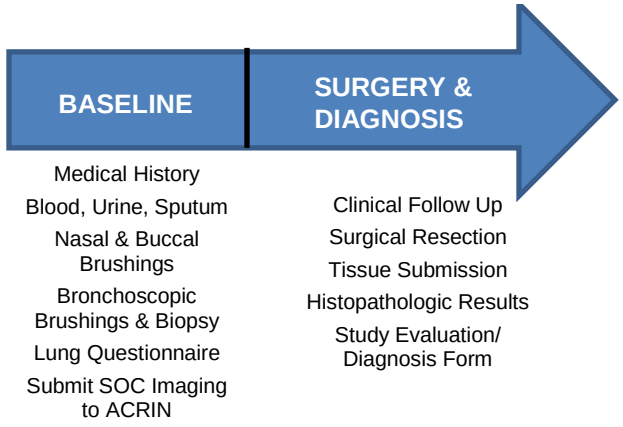
AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 4704

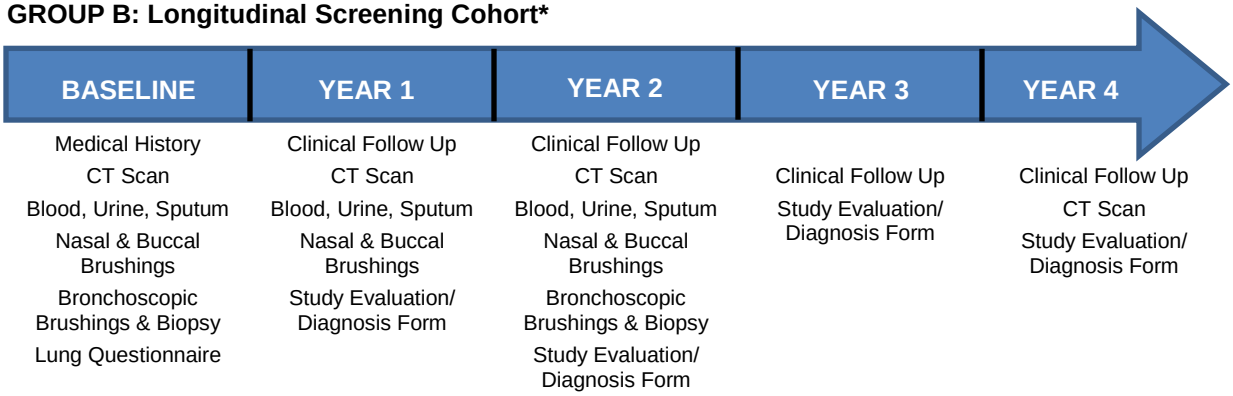
Detection of Early lung Cancer Among Military Personnel study 2 (DECAMP-2): Screening of Patients with Early Stage Lung Cancer and at High Risk for Developing Lung Cancer

Schemas

GROUP A: Cross-sectional Early-Stage Lung Cancer Cohort



GROUP B: Longitudinal Screening Cohort*



*** Should a Group B participant undergo surgery during the trial's four-year timeline, then surgical tissue samples will be required. If the participant is diagnosed with lung cancer during the trial timeline, then the Study Evaluation and Diagnosis Form will be completed at the time of diagnosis, no further study procedures will be conducted, but a final assessment of vital status and treatment/response will be required at year 4.**

STUDY OBJECTIVE

The goal of this project is to improve lung cancer screening in high-risk individuals by identifying biomarkers of preclinical disease and disease risk that are measured in minimally invasive and non-invasive biospecimens. Existing biomarkers for lung cancer diagnosis as well as new biomarkers discovered specifically in this clinical setting will be examined. Biomarkers that identify individuals at highest risk for being diagnosed with lung cancer prior to the appearance of concerning symptoms could increase the utility of lung cancer surveillance and the efficiency of lung cancer chemoprevention clinical trials. Achieving these goals would improve the detection and treatment of early stage and incipient lung cancer, while restricting the risk of these procedures to those individuals who currently exhibit the early molecular warning signs of impending disease.

ELIGIBILITY

This study will recruit two cohorts: a cross-sectional early stage lung cancer cohort (Group A) and a longitudinal screening cohort (Group B). The cross-sectional cohort will include 80 patients, with the intent of accruing 50 participants (Group A) diagnosed with early stage lung cancers and 30 control participants with benign lung disease. The longitudinal cohort (Group B) will include approximately 800 participants, current or former smokers with at least one additional risk factor of chronic obstructive pulmonary disease, emphysema, or family history of lung cancer, who are considered a high risk population based on a 10 year Bach risk model of lung cancer > 2.5%.

DECAMP-1 and DECAMP-2 are clinical studies developed under Department of Defense (DoD) and funded through the DoD Lung Cancer Research Program.

ABSTRACT

This protocol for human research study is conducted according to United States and international standards of Good Clinical Practice (International Conference on Harmonisation [ICH] Guidelines), applicable government regulations (e.g. Title 45, Part 46 Code of Federal Regulations) and the American College of Radiology Imaging Network (ACRIN) research policies and procedures.

Lung cancer is the leading cause of death from cancer in the US and the world, with cigarette smoking as its major cause. Lung-cancer associated mortality has remained essentially unchanged over the last 3 decades, in part because of our inability to detect lung cancer at its earliest and potentially curable stage. Military personnel have higher rates of smoking than the general population as well as exposure to other carcinogens, and there is a significantly higher incidence of lung cancer amongst military veterans. There is therefore an urgent need to develop new approaches for the early detection of lung cancer in this high-risk population. The broad goals of the DECAMP consortium are to develop and validate molecular biomarkers that can serve as tools for the early detection of lung cancer. While the recent National Lung Screening Trial (NLST) study demonstrated that screening for lung cancer by low-dose CT leads to a significant reduction of lung cancer specific mortality, biomarkers are needed to 1) determine which of the frequently detected lung nodules on computed tomography (CT) scan are malignant and 2) how to further define the large high-risk population that would be eligible for screening by CT to increase the efficacy of screening and to reduce the cost and morbidity associated with it. This study will discover and validate molecular biomarkers or the pre-clinical detection of lung cancer. In addition, the DECAMP consortium will establish a unique high quality biological (including bronchial airway brushings and biopsies, nasal and buccal brushings, blood, urine and sputum), clinical, and imaging repository from patients at military and Veterans hospitals across the US. All sites will acquire biosamples following the exact same standard operating procedures (SOPs) and these biosamples will be securely deposited in a central biorepository to support these studies and future correlative studies.

BACKGROUND AND SIGNIFICANCE

Background/Research Idea (DECAMP-2):

Biomarkers capable of preclinical detection of lung cancer could have clinical utility for referring patients to increased lung cancer surveillance, or chemoprevention, while sparing patients at low risk of developing lung cancer from unnecessary testing or treatment. As radiographic surveillance and chemoprevention trials are currently proposed for "high-risk" populations, a minimally invasive biomarker that could identify individuals with lung cancer prior to their presentation with clinical symptoms, or identify individuals with premalignant disease states which put them at higher risk for lung cancer development, might serve to increase the effectiveness of screening modalities. The potential utility of preclinical detection is multifold. 1) If the costs or risks associated with measuring biomarkers of preclinical disease are less than those associated with radiographic surveillance or other surveillance paradigms, then the use of preclinical lung cancer detection biomarkers would limit those costs and risks to the subset of highest-risk patients amongst the screening-eligible population. 2) Using preclinical lung cancer detection biomarkers to enrich for the subset of the screening-eligible population at highest-risk for having or developing lung cancer could decrease the false-positive fraction in subsequent lung cancer screening / surveillance modalities. 3) There are currently no proven agents for lung cancer chemoprevention and clinical trials to establish the effectiveness of proposed agents are hampered by the overall low rates of lung cancer. This necessitates studying potential chemoprevention agents in large cohorts with extended follow-up, and suggests that more accurate tools to assess lung cancer risk have the potential to dramatically streamline the evaluation of new therapeutics for lung

cancer chemoprevention. A clinical scenario in which those individuals at highest risk for lung cancer despite an absence of concerning clinical findings can be routinely identified promises to eventually change lung cancer from a disease that is detected late and treated surgically to a disease that is detected early and treated pharmacologically.

This study seeks to determine whether minimally invasive and non-invasive molecular biomarkers of lung cancer that were developed in the setting of high lung cancer prevalence have utility for distinguishing individuals with preclinical lung cancer or those at high risk for disease who will develop lung cancer from those who remain cancer free. The biomarkers to be tested in this context are the same bronchial airway and serum biomarkers for diagnosing lung cancer in patients with indeterminate pulmonary nodules as described in ACRIN 4703 DECAMP-1. Given the likelihood that the optimal biomarkers for detecting preclinical lung cancer or lung cancer risk might measure different biological processes than those that detect more advanced disease, and the likelihood that the collection of bronchial airway biospecimens may not be clinically justified in patients without clinical or radiographic manifestations of lung cancer, we will also seek to discover new biomarkers in serum and nasal epithelial cells from brushing the inferior turbinate that can be collected during routine clinic visits. These studies will address the DOD LCRP RFA clinical research areas related to a) development of a non-imaging-based screening protocol and b) combination of multiple detection/screening modalities.

STUDY OBJECTIVES/SPECIFIC AIMS

The goal of this project is to improve lung cancer surveillance in high-risk individuals by identifying biomarkers of preclinical disease and disease risk that are measured in minimally invasive and non-invasive biospecimens. Existing biomarkers for lung cancer diagnosis as well as new biomarkers discovered specifically in this clinical setting will be examined. Biomarkers that identify individuals at highest risk for being diagnosed with lung cancer prior to the appearance of concerning symptoms could increase the utility of lung cancer surveillance and the efficiency of lung cancer chemoprevention clinical trials. Achieving these goals would improve the detection and treatment of early stage and incipient lung cancer, while restricting the risk of these procedures to those individuals who currently exhibit the early molecular warning signs of impending disease. These goals will be accomplished though the following specific aims:

Primary Aims

- Discover new biomarkers from the cross-sectional cohort (Group A);
- Discover new genomic and proteomic biomarkers in the airway and blood for preclinical detection of lung cancer using the longitudinal cohort (Group B);

Secondary Aims

- Examine the change in biomarker values as a function of time prior to clinical diagnosis using the longitudinal cohort;
- Develop an integrated clinical and molecular model for the assessment of lung cancer risk using the combined cohorts;
- Validate the ability of biomarkers to detect prevalent disease and predicting incident disease in the longitudinal cohort (internal validation);
- Validate the ability of biomarkers to detect preclinical lung cancer in two independent screening cohorts (Nashville Early Detection of Lung Cancer Project and National Heart, Lung and Blood Institute Lung Health Study) that have airway and blood samples available (external validation). Examine the change in biomarker values as a function of time prior to clinical diagnosis.

STUDY OVERVIEW

The Detection of Early lung Cancer Among Military Personnel (DECAMP) consortium is a multidisciplinary and translational research program that includes 7 Veterans Administration Hospitals (VAH), the 4 designated Military Treatment Facilities (MTF) and 2 academic hospitals as clinical study sites, several molecular biomarker laboratories, along with Biostatics, Bioinformatics, Pathology and Biorepository cores. The DECAMP Coordinating Center will facilitate rapid selection, design and execution of clinical studies within this multi-institutional consortium. The ACRIN 4704 study will recruit two (2) cohorts to achieve the aims of this study: a cross-sectional early stage lung cancer cohort (Group A) and a longitudinal screening cohort (Group B).

Group A: The cross-sectional cohort (Group A) is an exploratory assessment group aimed at distinguishing patients with a history of cigarette smoking diagnosed with early stage lung cancer versus those with benign lung disease. We will recruit 80 patients undergoing resection surgery to Group A, with the intent of accruing 50 participants diagnosed with early stage lung cancer in order to compare them with 30 participants diagnosed with benign lung nodules who will act as a control cohort for this study. The biomarker assessments will help define biomarkers that are present at the earliest stages of disease and thus may potentially serve as screening tools in the future. We will include current or former cigarette smokers (≥30 pack-yrs, defined as number of packs per day x number of years smoked) who are 50 to 79 years old undergoing surgical resection for suspected early stage (stage 1) lung cancer. They must be willing and able to undergo fiberoptic bronchoscopy as pre-operatively or peri-operatively and be able to tolerate all biospecimen collection. We will exclude those with: a diagnosis of lung cancer prior to assessment for this resection surgery (i.e., some participants may be diagnosed with malignancy on bronchoscopic biopsy immediately prior to joining the study), contraindications to nasal brushing or fiberoptic bronchoscopy, and allergy to any local anesthetic that may be used to obtain biosamples in the study. After biospecimen collection, the cross-sectional cohort will have surgery, as prescribed. After submission of diagnostic results and tissue from surgical resection, no further study-related follow-up will be required for Group A after histopathologic assessment of the explant tissue to confirm malignancy or alternate diagnosis.

Group B: For this longitudinal screening cohort (Group B), we will enroll 800 participants who currently or historically smoked cigarettes and who have a 10 year Bach risk model of lung cancer > 2.5% (5). We will include participants 50 to 79 years old, with ≥10 cigarettes/day for at least 25 years' duration for current smokers, or ≥20 pack years for former smokers who quit 20 years ago or less. In order to further enrich for lung cancer risk, participants also will have COPD/emphysema or at least one first-degree relative with a diagnosis of lung cancer. We will exclude patients previously diagnosed with lung cancer. These patients will be followed for a total of 4 years with annual follow-up visits. A form describing current health status will be completed annually. Should a participant be diagnosed with lung cancer during the study timeline, the person will discontinue study-related procedures and, at year 4, the treating physician will need to complete a form describing vital status and treatment/response for the participant. We anticipate a 2% lung cancer prevalence rate (prevalent disease defined as that which is apparent on baseline CT scan or diagnosed within 6 months of enrollment) and a 1.5% annual incidence rate in this population. The ~50 lung cancer incident cases that develop over the follow-up period will be matched by clinical site to 50 participants who do not develop lung cancer during this same follow-up period, in order to provide a set of 100 participants for the biomarker studies.

PARTICIPANT SELECTION/ELIGIBILITY CRITERIA

Group A: Inclusion Criteria for cross-sectional early stage lung cancer cohort

- Ages 50 to 79 years;
- Smoking status: Current or former cigarette smoker with ≥ 30 pack years (PKY) (pack years = number of packs per day X number of years smoked);
- Undergoing surgical resection;
- Willing to undergo pre-operative or peri-operative fiberoptic bronchoscopy;
- Able to tolerate all biospecimen collection as required by protocol;
- Able to comply with standard-of-care procedures until surgery (approximately three months);
- Willing to allow standard-of-care imaging taken prior to study enrollment to be submitted to ACRIN;
- Able to fill out Patient Lung History questionnaire;
- Willing and able to provide a written informed consent.

Group B: Inclusion Criteria for longitudinal screening cohort

- Ages 50 to 79 years;
- Smoking status: Current or former cigarette smoker (≥10 cigarettes/day for at least 25 years' duration for current smokers, or ≥20 pack years for former smokers who quit 20 years ago or less)
- History of Chronic Obstructive Pulmonary Disease (COPD), emphysema, or at least one first-degree relative with a diagnosis of lung cancer;
- Willing to undergo fiberoptic bronchoscopy;
- Able to tolerate all biospecimen collection as required by protocol;
- Able to comply with standard-of-care follow-up visits, including clinical exams, diagnostic work-ups, and imaging for a maximum of four years or until diagnosis of lung cancer;
- Able to fill out Patient Lung History questionnaire;
- Willing and able to provide a written informed consent.

Exclusion Criteria

- Diagnosis of lung cancer prior to the current assessment (that is, patients are eligible for Group A if first lung cancer diagnosis has been recently confirmed by bronchoscopic biopsy and is leading to resection surgery, but not if this is not a first diagnosis);
- Contraindications to nasal brushing or fiberoptic bronchoscopy, including: ulcerative nasal disease, hemodynamic instability, severe obstructive airway disease (i.e., disease severity does not allow for

bronchoscopic procedures), unstable cardiac or pulmonary disease, as well as other comorbidities leading to inability to protect airway, or altered level of consciousness;

- Allergies to any local anesthetic that may be used to obtain biosamples in the study;
- Weight greater than that allowable by the CT scanner (**GROUP B ONLY**).

Inclusion of Women and Minorities

Both men and women and members of all ethnic groups are eligible for this study. In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993, with regard to inclusion of women and minorities in clinical research, the projected gender and minority accruals are shown below:

Gender and Minority Accrual Estimates for Combined Groups A and B

Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	18	69	87
Not Hispanic or Latino	159	634	793
Ethnic Category: Total of all subjects	**177**	**703**	**880**
Racial Category			
American Indian or Alaskan Native	4	9	13
Asian	3	17	20
Black or African American	27	112	139
Native Hawaiian or other Pacific Islander	3	9	12
White	140	556	696
Racial Category: Total of all subjects	**177**	**703**	**880**

STUDY PROCEDURES

Clinical, Imaging, and Biosample Acquisition

Participants will be enrolled into one of two cohorts for the study (Group A or Group B). A modified questionnaire from the NLST study will be administered to both Group A and Group B participants.

For the **Group A** cross-sectional early stage lung cancer cohort, biosample collection (e.g., nose, mouth, blood, sputum, and urine samples collections) will occur at the baseline study visit. However, bronchoscopic biopsy sampling and brushings for cell collection may be conducted immediately prior to resection surgery. The SOC imaging study used to determine need for surgical resection will be submitted to ACRIN. Group A participants will continue with SOC surgical resection and tissue collection for diagnosis. Diagnostic results will be reported to ACRIN. Surgical tissue will be collected for submission and histopathologic assessment towards study aims.

For the **Group B** longitudinal screening cohort, biosample collection (nose, mouth, blood, sputum, and urine samples) and results from routine clinical care (physical examinations, etc) will be obtained or collected at baseline and then annually through year 2. Low dose CT scans will be collected from within three months prior to enrollment or obtained at baseline, and then at years 1 and 2 after the baseline assessment and at the end of year 4 (i.e., none at year 3 for Group B in the study). The scan protocol for the low dose screening CT will be based on the protocol utilized in the NLST trial; the parameters will be provided in the ACRIN 4704 DECAMP-2 Imaging Manual. A Study Evaluation/Diagnosis Form will be completed annually unless the participant is diagnosed with lung cancer. If a participant is diagnosed with lung cancer, he/she will commence SOC treatment and the treating doctor will complete a form at year 4 describing vital status and treatment/response information. Should the participant undergo surgery during the 4-year study timeline, results and tissue samples will be submitted for the study.

The ACRIN Biospecimen Procedure Manual will include all procedures for biosample collection, processing, storage, and shipping procedures for Groups A and B.

Study Procedures Tables

Cross-sectional early stage lung cancer cohort (Group A) study table

GROUP A Study Procedure For Early Stage Lung Cancer Cohort	Eligibility/ Registration	Baseline	Follow up
Informed Consent Form	X		
Obtain Medical History	X		
Medical Record Review	X		
Screening/Eligibility Review	X		
ACRIN Web Registration	X		
Review and Submission of Institutional SOC Diagnostic Imaging	X		
Patient Lung History Questionnaire*	X	X*	
Pulmonary Function Test (May Collect from ≤3 Months Prior)		X	
Bronchoscopy: Brushing and Cell Collection Biopsy Tissue Collection		X†	X†
Blood Collection (Processing Timeline Defined Per Biospecimen Procedure Manual)		X	
Urine Sample Collection (Optional Processing as Defined in Biospecimen Procedure Manual)		X	
Nasal Brushing Collection		X	
Buccal Scraping Collection		X	
Sputum Sample Collection		X	
AE Assessment		X	
Physical Examination (SOC)		X	
Collect Data from Most-Recent Diagnostic Work Up (SOC)		X	
Surgery (if prescribed) and Tissue Submission			X
Study Evaluation/ Diagnosis Form			X

* Patient Lung History Questionnaire should be completed in full at baseline visit, starting the questionnaire and completing it either before or after any biospecimen collection occurring same-day.

† Bronchoscopic procedures for biopsy tissue sampling and brushing for cell collection may be completed at time of surgery instead of at the baseline visit.

Longitudinal high-risk cohort (Group B) study table

GROUP B: Study Procedure For Longitudinal Cohort	Eligibility/ Registration	Baseline	Follow Up			
			Year One	Year Two	Year Three	Year Four
Informed Consent Form	X					
Obtain Medical History	X					
Medical Record Review	X (for eligibility)	X (for data collection)				
Screening/Eligibility Review	X					
ACRIN Web Registration	X					
Review and Submission to ACRIN of Institutional SOC Diagnostic Imaging	X					
Patient Lung History Questionnaire*	X	X*				
Pulmonary Function Test (May Collect from ≤3 Months Prior at Baseline)		X	X	X	X	X
Bronchoscopy: Brushing and Cell Collection Biopsy Tissue Collection		X		X		
Blood Collection (Processing Timeline Defined Per Biospecimen Procedure Manual)		X	X	X		
Urine Sample Collection (Optional Processing as Defined in Biospecimen Procedure Manual)		X	X	X		
Nasal Brushing Collection		X	X	X		
Buccal Scraping Collection		X	X	X		
Sputum Sample Collection		X	X	X		
AE Assessment		X	X	X		X
Low Dose Helical CT Scan (May Collect from ≤3 Months Prior at Baseline)		X	X	X		X
Physical Examination (SOC)			X	X	X	X
Diagnostic Work Up (SOC) (Images and Data to Be Submitted)		X	X	X	X	X
Study Evaluation/ Diagnosis Form, Completed by Treating Physician†			X	X	X	X
Surgery, If Prescribed†		X	X	X	X	X

* Patient Lung History Questionnaire should be completed in full at baseline visit, starting the questionnaire and completing it either before or after any biospecimen collection occurring same-day.

† Should a Group B participant undergo surgery during the trial's four-year timeline, then surgical tissue samples will be required. If the participant is diagnosed with lung cancer during the trial timeline, then the Study Evaluation and Diagnosis Form will be completed at the time of diagnosis, no further study procedures will be conducted, but a final assessment of vital status and treatment/response will be required at four years.