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TITLE: Further Development of an Exhaled microRNA Biomarker of Lung Cancer Risk

PRINCIPAL INVESTIGATOR: Dr. Simon Spivack

**RECIPIENT: Albert Einstein College of Medicine, Inc.
Bronx, NY 10461**

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Fort Detrick, Maryland 21702-5012**

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14. ABSTRACT We seek to devise a non-invasive airway based exhaled microRNA metric for lung cancer risk, initial work to be tested in a case control study. We expanded the microRNA panel to ~30 microRNAs, and expanded the cohort beyond Einstein-Montefiore/Bronx to include Bronx / JPeters VAH clinic-based recruits, in a case-control study. We also expanded the assessment of lung cancer subjects to also include limited (3-month) prospective follow-up of non-cancer controls in order to minimize control contamination/misclassification, and improved matching on age, smoking status, and underlying COPD (initial n~90 versus n~90 controls). In essence we were able to detect a discriminant signature from exhaled microRNAs, whereby discriminant accuracy over and above clinical criteria alone, was improved by 3-8%. There data are being verified now, and we have added in several microRNAs to the panel. WE are also recruiting individuals from a CT screening cohort, for our next validation stage, although recruitment from this cohort is tactically challenging given current resources, and therefore slower than					
15. SUBJECT TERMS Lung cancer early detection; exhaled biomarkers; microRNAs.					
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1. **INTRODUCTION:** Lung cancer screening, as currently devised, is somewhat inefficient as it is not focused on those at highest risk of lung cancer, and thus yields many false positives. Acquired somatic changes may offer molecular measures of that risk, and if airway based, may be more lung-specific. Since microRNA deregulation is a common derangement in many disorders, including cancer, we hypothesize that exhaled microRNAs may be incrementally valuable for assigning risk, and therefore for leveraging the efficiency of screening CT or other disease detection efforts. Initial work has been devised as cross-sectional, an exhaled microRNA panel to be tested in a case control study. As of July 2017, we expanded the microRNA panel to ~30 microRNAs, and expanded the cohort beyond Einstein-Montefiore/Bronx to include Bronx / JPeters VAH clinic-based recruits, in a case-control study. We also expanded the assessment of lung cancer subjects to also include limited (3-month) prospective follow-up of non-cancer controls in order to minimize control contamination/misclassification, and improved matching on age, smoking status, and underlying COPD. Fledgling efforts to enroll members of a CT screening cohort were initiated.

2. **KEYWORDS:** Lung cancer early detection; exhaled biomarkers; microRNAs.

3. **ACCOMPLISHMENTS:**

- **What were the major goals of the project?**

The Specific Aims to be addressed during the two-year LCRP Expansion Award project are:

Aim 1. Expand the Einstein-Montefiore/Bronx to include VAH clinic-based case-control study. Expand the assessment of lung cancer subjects pre-resection to also include limited (6-month) prospective follow-up of non-cancer controls in order to minimize control contamination/misclassification, and improve matching on age, smoking status, and underlying COPD (n=150 versus n=150 controls).

Aim 2. Engage the Montefiore CT screening prospective cohort, whereby among a nested case-control study of those who qualify by National Lung Cancer Screening Trial (NLST) criteria, patients undergo three serial CT scans (baseline and two subsequent annual scanned) according to protocol. A subset with CT-indeterminate (NCN) nodules gets immediately biopsied or observed/additionally re-imaged per clinical indication.

- **What was accomplished under these goals?**

TASK	TECHNIQUE	THROUGHPUT	ORIGINALLY	TOTAL	Percent
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		calculation	ESTIMATED MONTHS	GOAL	Completed (as of Aug 01, 2017)
IRB Approval			Montefiore: by month 0; VAH: by month 2.	NA	Completed MMC month 0; Completed Bronx VAH month 5
USAMRMC Human Research Protection Office (HRPO)			Montefiore by month 2; VAH by month 4	NA	Delayed, Completed VAH by ~month 8 (late spring 2017)
<u>AIM 1</u>			months 1-16		
Recruitment, Aim 1	<u>Clinical setting:</u> (i) pre-bronchs, (ii) pre-resections, (iii) comp.controls	Site 1 (Einstein-Montefiore existing, to-be-pulled samples ets): 75 cases+75 controls Site 2 (Bronx VAH): ~75 cases+~75 controls	months 1-3; months 4-16	150 150	Montefiore 125% (accrual exceeding estimate) completed month 3 Bronx VAH 25% accrual completed
EBC collection	Rtubes®	One per subject, 300 case-control subjects;	months 1-16	300	67% completed
Exhaled microRNA-PCR	MicroRNA-qPCR	Aim 1: 150+150=300 EBC samples x 40 miRs each	months 6-18	12,000*	EBC completed 67% analysis to date
Expectorated airway specimen (sputum) collection and analysis	MicroRNA-qPCR	Aim 1: 75+75=150 clinical case-controls x 10 top microRNAs;	months 1-16	1,500*	Sputum 0% analyzed
microRNA target affirmation	MicroRNA-affinity pull-down	Aim 1: 5 transcripts x 100 RT-PCRs each (and 100 sequenced clones each)	months 13-16	500 (and 500 Sanger-seq clones)	0% pull-down complete
	TECHNIQUE	THROUGHPUT calculation	ORIGINALLY ESTIMATED MONTHS	TOTAL GOAL	Percent Completed (as of Aug 2017)
AIM 2					
Recruitment	Cohort setting: Baseline CT screening; cases and controls	Site 1 (Montefiore): 50 cases+150 controls Site 2 (Bronx VAH): 0 cases + 0 controls	months 1-20	200 0	5% completed
EBC collection (and sputum)	Rtubes®	200 nested CT screening cohort case-control subjects.	months 1-20	200	5% completed
Exhaled microRNA-PCR	MicroRNA-qPCR	Aim 2: 50+150=200 prospective cohort sample sets x 20 top miRNAs	months 20-24	4,000*	0% completed
Expectorated airway specimen (sputum) collection and analysis	MicroRNA-qPCR	Aim 2: 25+75=100 prospective cohort sample set collection. Analyze x 10 top miRNAs	months 1-20 collect Months 20-24 analyze	100 1,000*	0% completed

Case-control studies of exhaled microRNAs, July 15, 2016 – July 2017:

We have been piloting the case-control discrimination, and technical sensitivity, specificity, and anatomic surrogacy of these EBC specimens for the deep lung (i.e., BAL and bronchial BB), in work funded by this DoD/CDMRP/LCRP, and prior grants.

Initial case-control studies of exhaled microRNAs: We have recently been piloting the case-control discrimination, and technical sensitivity and specificity of these EBC specimens for the deep. We constructed a panel of 35 microRNAs applied to EBC from a small clinical set of 44 early stage (I and II) cases and 45 controls (Group D, 89 total individuals). The *qualitative* RT-PCR data was analyzed in two different ways, first by logistic regression, and then by random forests (RF). Both analyses revealed a small set of miRs (Fig. 12, column 1) that carry overall case-control discriminant over the pre-selected clinical factors (age, smoking status, COPD presence) alone, shown for adenocarcinoma cases. In a second replicate small clinical case-control series of 41 early stage cases and 47 controls, *qualitative* exhaled microRNA data for Group E, 88 individuals), a small set of miRs (Fig. 12, column 2) improved the discriminant AUC of clinical factors alone. Combining both sub-studies (groups D+E, n=177), case-control discrimination improved from clinical factors (age, smoking status, COPD) alone *vs.* clinical factors *plus* exhaled microRNAs by 3-6%; similar prediction increments (3-8%) were found for all NSCLC histologies combined (not shown).

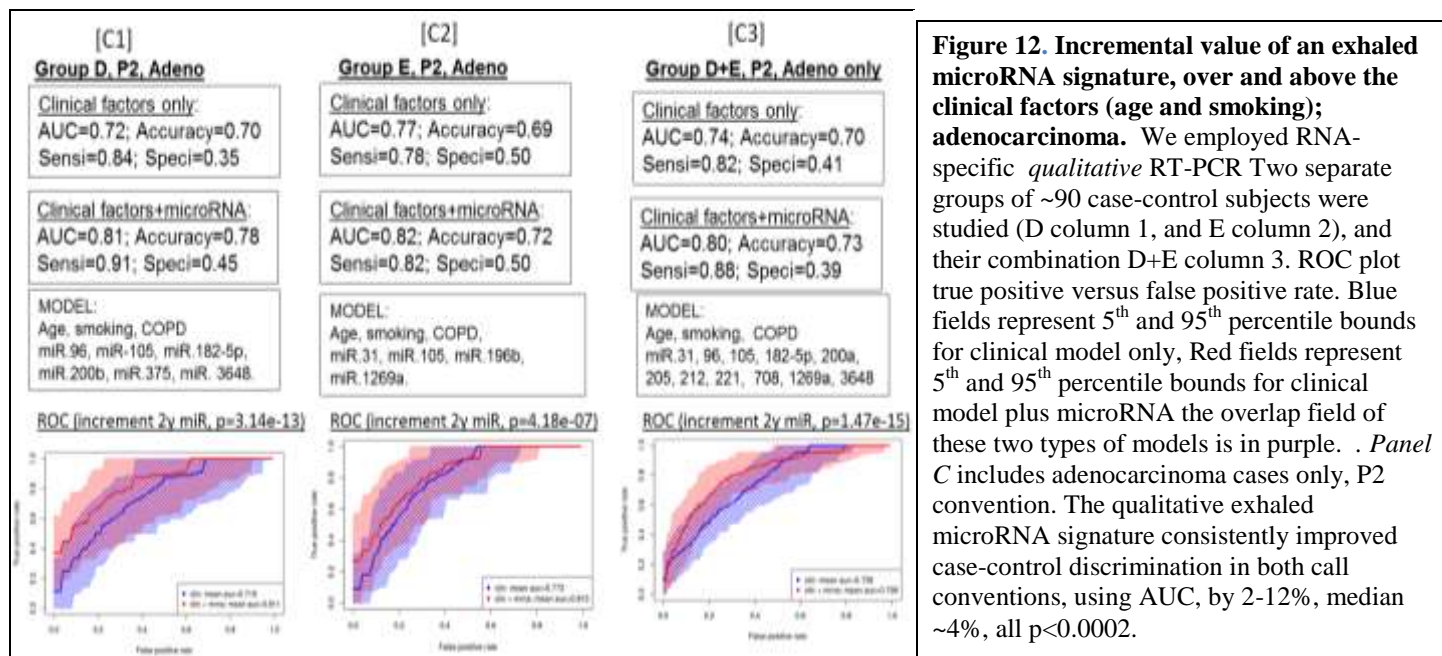


Figure 12. Incremental value of an exhaled microRNA signature, over and above the clinical factors (age and smoking); adenocarcinoma. We employed RNA-specific *qualitative* RT-PCR. Two separate groups of ~90 case-control subjects were studied (D column 1, and E column 2), and their combination D+E column 3. ROC plot true positive versus false positive rate. Blue fields represent 5th and 95th percentile bounds for clinical model only, Red fields represent 5th and 95th percentile bounds for clinical model plus microRNA the overlap field of these two types of models is in purple. . Panel C includes adenocarcinoma cases only, P2 convention. The qualitative exhaled microRNA signature consistently improved case-control discrimination in both call conventions, using AUC, by 2-12%, median ~4%, all p<0.0002.

▪ **Include a discussion of stated goals not met.**

We have had trouble recruiting from the CT screening cohort at our institution, because of tactical challenges in capturing/interfaces with the 25% of individuals screened who have nodules, and particularly those with higher risk nodules. These short-term follow-up CT studies for LungRads 3 and 4 nodules are not concentrated in a given campus location in our system, not clustered in a given time. Therefore capturing them, given the fluidity of patient scheduling and limited personnel budgetted in this proposal, even with the help of volunteer research coordinators, has been very challenging. Therefore, Aim 2 is unlikely to be complete by summer 2018, end of term for this proposal.

▪ **What opportunities for training and professional development has the project provided?**

Name: Bianca Ho
 Role: Medical student on summer 2017 research elective.
 Person months: 1.5 months this year (volunteer)
 Contribution to Project: Ms Ho was testing RT-PCR of microRNAs optimization

▪ **How were the results disseminated to communities of interest?**

Oral presentation at American Thoracic Society meeting, spring 2017, reporting to peer pulmonologists and researchers.

▪ **What do you plan to do during the next reporting period to accomplish the goals?**

This next period (Aug 2017-February, 2018): We have been working on improving subject accrual at the Bronx VAH, including sputa. We in parallel have been optimizing RT-PCRs on an additional n=5 set of newly identified microRNAs that we have been informed are case-control discriminant on bronchial brushings (per Spira et al). With the augmented sampleset, and re-interrogation with the new miRs, we are working to re-interrogate the n>200 EBC sampleset for better case-control discrimination. We will be interrogating the sputum collected in the next 6-12 months. We are redoubling strategies for Aim 2 accrual, by electronic tracking of screenees.

4. **IMPACT:**

▪ **What was the impact on the development of the principal discipline(s) of the project?**

We have demonstrated that the airway is accessible by non-invasive exhaled means for this and other (smaller) analytes that might reflect lung pathology, or risk for lung pathology. This is an important demonstration, irrespective if our signature discriminates lung cancer case from control individual, or indeed can predict future incident disease.

▪ **What was the impact on other disciplines?**

We have demonstrated that the airway is accessible by non-invasive exhaled means for this and other (smaller) analytes that might reflect lung pathology, or risk for lung pathology. This is an important demonstration, for other types of lung disease..

▪ **What was the impact on technology transfer?**

Nothing to report. However the demonstration enables the eventual development of non-invasive airway-based strategies for detecting lung disease risk or presence, potentially important intellectual property for eventual public use.

▪ **What was the impact on society beyond science and technology?**

Nothing to report. However the demonstration enables the eventual development of non-invasive airway-based strategies for detecting lung disease risk or presence, potentially important intellectual property for eventual public use.

5. **CHANGES/PROBLEMS:**

▪ **Changes in approach and reasons for change**

We are redoubling strategies for Aim 2 accrual, by electronic tracking of screenees.

• **Actual or anticipated problems or delays and actions or plans to resolve them**

We are redoubling strategies for Aim 2 accrual, by electronic tracking of screenees. It took a long time (8 months) to get recruitment underway at VAH, largely due to an IRB delay of ~5-6 months, and then a CDMRP period before approval of protocol at VAH, and therefore entire protocol. Therefore, that VAH projection lags initial projections.

▪ **Changes that had a significant impact on expenditures**

Nothing to report.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

Nothing to report.

- **Significant changes in use or care of human subjects**

Nothing to report.

- **Significant changes in use or care of vertebrate animals.**

N/A.

- **Significant changes in use of biohazards and/or select agents**

N/A.

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

Nothing to report.

- **Publications, conference papers, and presentations**

- **Journal publications.**

Nothing to report.

- **Books or other non-periodical, one-time publications.**

Nothing to report.

- **Other publications, conference papers, and presentations.**

Han W, Keller S, Gombar S, Suh Y, Aldebagh M, Malik S, Hosgood D, Wang T, Pradhan K, Spivack, SD. Non-invasive risk biomarkers for lung cancer: An exhaled microRNA panel interrogation and validation. American Thoracic Society, International Conference, Wash, DC, A30, May 21, 2017, Poster Discussion A30, Abstract 1255.

- **Website(s) or other Internet site(s)**

Nothing to report.

- **Technologies or techniques**

Nothing to report, until a predictive exhaled microRNA signature is validated..

- **Inventions, patent applications, and/or licenses**

Nothing to report.

- **Other Products**

Nothing to report, other than some ~35 additional VAH EBC specimens, and ~25 VAH EBC--sputum biospecimen pairs.

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

- **What individuals have worked on the project?**

EINSTEIN/MONTEFIORE:

Name: Simon Spivack, MD. MPH

Role: PI

Person months: 0.72 months this year (6% effort)

Contribution to Project: Dr. Spivack is the PI, directing the subject accrual, EBC sample extraction, microRNA panel optimization, RT-PCR optimization, data analyses.

Name: Miao Shi, PhD

Role: Technician

Person months: 6.0 months this reporting year (50% effort)

Contribution to Project: Dr. Shi is the person performing the EBC sample extraction, optimization, RT-PCR optimization

Name: Bianca Ho

Role: Medical student on summer research elective

Person months: 1.5 months this reporting year (volunteer)

Contribution to Project: Ms Ho was testing RT-PCR of microRNAs optimization

Name: Mohammad Aldabagh, MD

Role: Volunteer research assistant

Person months: 5.0 months this reporting year. (volunteer)

Contribution to Project: Dr. Aldabagh was organizing samples and recruitment.

Name: Dhruv Patel, MD
 Role: Volunteer research assistant
 Person months: 1.0 months this reporting year. (volunteer)
 Contribution to Project: Dr. Patel was organizing samples and training in patient recruitment.

JAMES PETERS BRONX VAH:

Name: Robert Siegel, MD
 Role: Co-PI, VAH
 Person months: 0.18 months this quarter (6% effort)
 Contribution to Project: Dr. Siegel is the VAH site-PI, directing the subject accrual, EBC and sputum sample collection at the VAH.

Name: Alison T Keller, RN
 Role: Research coordinator, VAH
 Person months: 2.0 months this year
 Contribution to Project: Ms Keller is the VAH site-coordinator, executing the subject accrual, EBC and sputum sample collection at the VAH.

▪ **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

.ACTIVE=>COMPLETED GRANTS

1 R21 CA192168-01 (Spivack)	12/01/14-11/30/16 (+1yr NCE)	1.2 calendar months
NIH/NCI	\$150k direct/initial yr	

Exhaled breath microRNAs for determining lung cancer risk assessment.
 The goal is to validate a panel of rationally-sifted preneoplastic lesions to determine which exhaled microRNAs can serve as lung cancer risk biomarkers in both case-control and prospective cohort settings.
 Role: PI, Effort 1.2 calendar months..No overlap.

1R01-CA180126-01 (MPI-Vijg, Suh, Spivack)	07/01/13-06/30/17 (+1 yr NCE)	0.96 calendar months
NIH-NCI-Provocative Questions	\$ 407K (155K direct/yr, Spivack Lab)	

“Age-cancer interplay of genome and epigenome in human lung”
 The goal is to define at a whole genome level the somatic mQTL and eQTL changes, and related germline variants, in the aging lung underlying lung carcinogenesis in humans.
 Role: Co-PI (MPI), Effort 0.96 calendar months. No overlap.

U01OH010993-01 (Aldrich=>Spivack)	07/01/15-06/30/17.(NCE)	1.8 calendar months
NIOSH/CDC		

Clinical characteristics and outcomes of WTC-associated sarcoidosis.
 The goal is to characterize the higher-than-expected sarcoidosis rates, and our specific part is to explore genetic variants via candidate gene/promoter sequencing possibly underlying this variability. Role: Co-Investigator at 0.6 months=>PI 1.8 months. No overlap.

PENDING=>ACTIVE/FUNDED GRANTS:

1R21CA209436-01A1 (MPI Spivack/Vijg)	09/01/17-08/31/19	1.2 calendar months
NIH-NCI		

Methylome characterization of bronchial epithelial progenitor cells
 The goal is to determine the methylomic features of normal appearing bronchial epithelial cells from lung cancer cases *versus* that of controls, to determine whether cases have basal bronchial progenitor cells signatures of being poised for pro-carcinogenesis. No overlap.

▪ **What other organizations were involved as partners?**

Organization Name: James Peters Bronx VAH

Location of Organization: Bronx, NY, USA

Partner's contribution to the project: Subject accrual site, case-control study.

Collaboration Subject accrual site, case-control study.

8. **SPECIAL REPORTING REQUIREMENTS**

- **COLLABORATIVE AWARDS:** Bronx VAH activities are included in this report.

9. **APPENDICES:**

Nothing to append.

Clinical Research Protocol: **GENETICS OF LUNG DISEASE**

Principal Investigator: **Simon Spivack, MD, MPH**

CCI#: **2007-407**

Locations/ Sites: Albert Einstein College of Medicine, Weiler Hospital and Moses Division of Montefiore Medical Center

Proposed number of subjects to enroll: 2000

Funding: National Institute of Health

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INTRODUCTION

This research study is a lung cancer case *versus* control (no lung cancer) comparison evaluating four issues.

- 1) To identify specific molecular events common to individuals with lung cancer and other lung diseases.
- 2) The degree to which the molecular genetic events of human lung carcinogenesis and other lung disease may parallel genetic events found in more easily accessed surrogate tissues, such as sputum, saliva, buccal cells, exhaled breath, and blood.
- 3) To identify markers of disease risk or prognosis for lung cancer and other lung disease.
- 4) To determine group EBC DNA methylation Patterns by high resolution tagged bisulfate genomic sequencing of three tumor suppressor genes (DAPK, RASSF1A, PAX5B), according to smoking status (current, former, never), and lifelong dose (pack years) in a sample of HIV-infected smokers.

These four goals anticipate attempts at molecular screening strategies for early detection of lung cancer, and other lung diseases.

PURPOSE

This research study is designed to explore pathways, genes and molecules that may be responsible for the susceptibility and/or development of lung disease in anticipation of establishing molecular screening strategies for the early detection of lung diseases, including cancer.

This research will attempt to establish a relationship between the molecular changes that occur in cells from the mouth, saliva, exhaled breath and blood as they relate to the development of lung disease. If this relationship can be proven, it may be possible in the future to test for certain lung diseases with a simple laboratory test. Dr. Simon Spivack, the principal investigator, is conducting a research investigation to determine whether the activity of certain genes and proteins in the lung and other tissues increases with exposure to cigarette smoke or other environmental hazards. This increased activity might impact the development of lung cancer and other diseases. Genes instruct proteins to control and direct many activities of cells in the human body. The genes of interest to this investigation include inhaled foreign compound- processing genes, certain cancer-associated and inflammation associated genes, and other genes, proteins and biological markers associated with the metabolism of foreign substances. The activity of genes and proteins found in the lung are thought to parallel that detected in blood, saliva, exhaled breath condensate (moisture) and mouth cells. This is unproven. Additionally, the relationship of these genes' activity to lung disease remains unproven.

The following is a list of genes for which DNA methylation, gene expression, or other alterations are currently being studied or is planned for study:

Ahr, ARNT, Nrf1-2, AP1, SP1, ERalpha, ERbeta, CYP1A1, CYP1B1, CYP2A13, CYP3A4, CYP3A5, GSTM3, GSTP1, GSTT1, SULT1-4, NQO1, CAT, GPx, GLCLC, SOD1, MRP1-10, BCRP, OGG, XRCC1- 4, ERCC1-4, NBS1, XPC, XPD, XPF, UNG1-2, MUG1-2, TDG, MBD1-4, MPG, MYH, NTH1-2, p53, kRas, p21, RASSF1A, PAX5B, CDH1, MGMT, p16 and other carcinogen and oxidant metabolism, DNA repair, cell cycle and other relevant carcinogenesis and inflammation related genes.

Selected lung specimens will also be shared with collaborating laboratories, for the purposes of: (a) tumor heterotransplantation into animals to test novel therapeutics and biomarkers; (b) testing for progenitor/stem cells in lung cancer; (c) other purposes by future collaboration.

- (a) The understanding of the molecular determinants of lung cancer development has evolved significantly over last several years. Several molecular markers have helped clinicians and scientist better understand and treat different subtypes on lung cancer. With the advent of many new chemotherapies and targeted therapies, it is becoming of paramount importance to understand the molecular changes in the individual tumor and develop effective targeted therapies.

One way to achieve this insight for personalized medicine, and improved chemotherapy, is through the heterotransplant model, where a small fragment of human tumor is implanted in nude mice. This allows investigators to study a variety of different chemotherapies and targeted therapies and to identify markers that will determine response to individual treatments. This type of approach has been well studied with traditional chemotherapies and has a very high correlation with clinical response rate. The heterotransplant platform give us a unique platform to further understand the molecular origins of lung cancer and will enable us to test the use of these as biomarkers to determine the response to new emerging targeted therapies. This will be done in collaboration with our co-investigators Dr. Piperdi and Dr. Perez-Soler from department of medical oncology.

- (b) Another type of study, to understand the role of stem cells in carcinogenesis, and tumor biology, involves determining the presence and behavior of stem cells. These are “outgrown” from small samples of the already surgically removed lung tissue. The cells’ behavior has implications for anticancer strategies. They are grown over generations, donor identity is not known to investigators, and therefore no linkage to identity is available. This aspect of the study will be done in collaboration with Dr. Yakov Peter of Yeshiva University.

SELECTION OF PATIENT POPULATION

- Group 1: Patients at least 21 years of age that have been seen and evaluated by a pulmonologist and are scheduled to undergo elective surgical lung biopsy or surgical resection for diagnostic/therapeutic purposes. (3 digit subjects)
- Group 2: Patients at least 21 years of age that have been seen and evaluated by a pulmonologist and are scheduled to undergo elective bronchoscopy for diagnostic purpose. (3 digit subjects)
- Group 3a: Subjects at least 21 years of age that have no known diagnosis of lung cancer will be enrolled as a control group. These subjects do not donate lung tissue itself, but do donate non-invasively-collected surrogates (blood, saliva, exhaled breath condensate, and mouth/buccal cells. (4 digit subjects)
- Group 3b: Subjects at least 21 years of age who are undergoing short term (nearly 3 months) follow up CT scan for a nodule/mass detected on initial/annual CT scan screening for lung cancer, will be enrolled as another control group. These subjects do not donate lung tissue itself, but do donate non-invasively collected surrogates (blood, saliva, exhaled breath condensates and mouth/buccal cells. (4 digit subjects).

Group 4: Subjects at least 21 years old with known HIV positive status. This group will donate exhaled breath condensate on two separate visits, complete a questionnaire, provide saliva and undergo exhaled carbon monoxide testing.

Group 5: Patients at least 21 years of age that have been seen and evaluated by a pulmonologist and are scheduled to undergo elective bronchoscopy for diagnostic purposes. This is a subset of group 2 with subjects consenting for more than 4 bronch brushes up to a maximum of 15 (3 digit subjects).

INCLUSION/EXCLUSION

Inclusion Criteria:

- Age: minimum age of 21 years
- Gender: Male and Female adults
- Ethnicity: All ethnic groups and races.
- Subjects undergoing bronchoscopy for diagnostic purposes or therapy.
- Subjects without a known diagnosis of lung cancer who are not scheduled for lung tissue collection procedures.

Addition Inclusion Requirements for Group 4 only: Immunologically or virologically confirmed HIV infection.

Exclusion Criteria:

No invasive research specimens (BAL/biopsy) will be obtained from bronchoscopy subjects with evidence of bleeding diathesis or known coagulopathy precluding clinically-indicated biopsy (e.g. INR>1.3, PTT>1.3), thrombocytopenia <50k, uremia with serum creatinine >3.0, unstable angina, recent myocardial infarction (within 3 months), uncontrolled congestive heart failure or severe pulmonary hypertension (mean PAP>75 mmHg).

DISCONTINUATION

Subject or Attending Physician request that the patient be withdrawn from the study.

DATA SAFETY MONITORING PLAN

Two Pulmonary Medicine clinicians, not associated with the protocol, will monitor for adverse events, and study subject concerns. Neither is a collaborator/consultant/advisor, nor has a direct interest in the protocol. The committee will include:

1. **William N. Rom, MD, MPH**
Division Chief, Pulmonary & Critical Care Medicine, NYU Medical Center
2. **Timothy Harkin, MD**
Interventional Bronchoscopy Service
Pulmonary & Critical Care Medicine, Mt. Sinai Medical Center, New York City.

The committee shall meet prior to enrolling research participants. They will be informed of minor adverse events on a regular (q 6- month) basis, and of more serious adverse events when they occur.

SOURCES OF RESEARCH MATERIAL

1. **LUNG TISSUE** (described in detail in nih grant proposal)

1) Surgical lung harvest

Procedure: Lung resection specimens, which are not needed for clinical/pathologic diagnosis and which are normally discarded, will serve as the main source of surgical lung tissue.

One specimen obtained will be cancer/involved (tumor) or benign/involved (if non-cancer such as granulomas, fibrosis, etc.) tissue, and the other will be a non-cancer (non-tumor/non-involved, adjacent) specimen. Both of these two specimens will be placed in labeled vials containing an appropriate preservative, flash frozen within 15 minutes of surgical ligation, and placed at -70°C in the tissue bank at AECOM, for ultimate storage in the Spivack laboratory liquid N₂ tissue repository. However, selected lung specimens will be shared with collaborating laboratories, as described above, for the purposes of: (a) tumor heterotransplantation into animals to test novel therapeutics and biomarkers; (b) testing for progenitor/stem cells in lung cancer; (c) other purposes by future collaboration.

Risk: None. Surgical risk is unaffected by the study, as no alterations of the surgical procedure, nor additional tissue, is taken for research purposes. Physical risk is none incremental to that inherent to post-operative recovery. Inconvenience of an interview and surrogate tissue collection is the risk associated with the study itself.

Benefit to subject: None.

2) Bronchoscopy

Endobronchial biopsies (EBBx) (Consenting subjects undergoing fiber optic Bronchoscopy)

Purpose: To study the gene expression and epigenetic features of putative lung cancer risk genes in uninvolved bronchial mucosal tissue, as opposed to whole lung, in those with malignant and nonmalignant lung disease. This is best accessed by endobronchial brush or biopsy.

Procedure: All eligible consenting adults undergoing elective, non-emergent, non-ICU bronchoscopy at AECOM associated institutions would have four additional endobronchial biopsies performed under direct visual guidance, of visually non-involved areas of the proximal bronchial tree (2nd - 4th order bronchi). These four endobronchial bronchoscopic biopsies (which are in addition to, and taken after, any endobronchial specimens obtained by the pulmonologists for clinical purposes) will be taken as follows: (a) One of the specimens obtained will be from visually apparent cancer (tumor) tissue; and (b) The other three will be from non-cancer (non-tumor) airways. Several of the bronchoscopic lung biopsies from non-tumor tissue may be collected using a bronchoscopic brush. This brushed epithelium method of specimen collection has less associated risk to subjects than does endobronchial tissue forceps biopsy, and much less than transbronchial biopsy. Potential complications, where publications do exist, are described below.

Risk: Common: *Prolonged procedure.* Time added for extra brushing is about 1 minute per brush or 2 minutes for forceps, x 4 specimens= 4-8 minutes which should not affect duration of anesthesia (which is topical+parenteral conscious sedation).

Rare: *Bleeding:* (reported on a per procedure basis, not reported on a "per bite" basis). Minimal attributable incremental risk for bleeding associated with the fifth through eight endobronchial biopsy (not reported as incrementally risky in literature or our experience.) There is less physical risk to subjects who have the bronchoscopic brushing, which is not well estimated in literature. Bleeding complications are not typically listed specific to endobronchial biopsy itself, and certainly not specific to endobronchial brush specimens. A March 2008 review of literature update reveals no additional studies that breakdown that risk since the last search several years ago. In one study (Dransfield, 2003), the overall complication rate in a high-risk lung transplant population from conventional bronchoscopy included those procedures entailing endobronchial forceps (EBBx) and transbronchial forceps (TBBx) biopsies; a rate of 0.14% for major bleeding, and 0.28% for minor bleeding was reported. In another study, 17 total endobronchial forceps biopsy-induced bleeding episodes per 3096 bronchoscopy procedures with any type of biopsy (TBBx or EBBx) = 0.54%. EBBx termed "less likely to cause significant bleeding" than

TBBx so EBBx bleeding rate is likely less than 0.54% per multiple-biopsy procedure. For example, other authors report TBBx bleeding rate is 2.8% in TBBxl (not EBBx) biopsies (Pue 1995, HernandezBlasco LH, 1991). (3 of the 3096 bronchoscopic procedures were marked by "profuse bleeding", requiring nonsurgical interventions such as intratracheal instillation of topical epinephrine, or bronchoscope tamponade of the area (0.1%). The other 14 were minor or moderate, and resolved spontaneously within minutes. Risk factors for TBBx - and/or EBBx - induced bleeding are controversial, (Cordasco EM et al. Chest 1991) but may include clinical history of bleeding with invasive procedures, thrombocytopenia, coagulopathy, uremia, pulmonary hypertension, malignancy (remote or chest), and immunocompromised status.

Pneumothorax: (reported on a per procedure basis, not reported on a "per bite" basis) Not reported specifically for endobronchial forceps (EBBx) biopsy, and not reported for endobronchial brush (cytologic) sampling. The rates for EBBx under direct visual guidance are expected to be much less than the 0.3-0.7% rate that are estimated from those for TBBx (a much higher risk, fluoroscopically-guided procedure, for pneumothorax), the rates have ranged from 0.7 – 5.5% in larger series for TBBx. Collapsed lung from the extra bronchial samples procured for research (inferred as less than 0.30%) could result in the need to reinflate the lung, with a surgically-placed chest tube, over approximately a three-day admission to the hospital. There could be pain or discomfort associated with this rare event. We have now employed these research EBBx brushings in >200 clinical bronchoscopies, with n=0 adverse effects clearly related to this research procedure.

Benefit to subject: None.

Bronchoalveolar lavage (BAL)

Purpose: The procedure is designed to obtain (diluted) bronchiolar and alveolar lining fluid to detect DNA modification such as CpG methylation, for the purpose of determining the anatomic airway origin (pharynx versus major bronchi, versus bronchiole/alveoli) of exhaled DNA.

Procedure: Bronchoalveolar lavage is "piggy-backed" on clinically indicated bronchoscopies. This is incremental to bronchoscopy itself, and is a minimally invasive diagnostic technique involving the suffusion of up to five 20 cc aliquots of sterile saline into the mid-distal airways by wedging the bronchoscope and immediately retrieving that saline sampling of the distal bronchoalveolar tree. For consenting subjects having bronchoscopy for clinical indications, bronchoalveolar lavage (BAL) for research purpose will be performed after any clinically indicated biopsies.

Risk: Minimal. BAL is a routine clinical procedure, employed at >50% of all bronchoscopies, and does not result in any complications in approximately 95% of patients. Of the remaining ~5%, most complications are minimal and include transient (seconds-minutes) decrease in baseline *PaO2*, transient fever (2%), cough (~1%), transient chills (<1%), bronchospasm(<1%). Life threatening complications occur very rarely, estimated at <0.01%.

Benefit to subject: None

Overall, pneumothorax from BAL or endobronchial biopsy alone is rare. One clinical study in hematologic malignancy subjects showed no events in 45 subjects undergoing BAL alone (Mulabecirovic, 2004). Another study of research subjects undergoing endobronchial biopsy (n=98) or endobronchial biopsy combined with BAL (n=68) showed one pneumothorax in a subject with severe emphysema (Hattotuwa, 2002). In a clinical study of ~1300 children undergoing bronchoscopy outside of the intensive care unit for clinical indications, one pneumothorax requiring a chest tube insertion was noted in a child with bronchiectasis

undergoing endobronchial biopsy. Other electronically available studies in the last 12 years do not allow one to extract a pneumothorax rate specific to these three non-transbronchial biopsy procedures (Bronchoscopy, Endobronchial biopsy, and Bronchoalveolar Lavage (BAL)).

We have now employed these research BAL procedures in >200 clinical bronchoscopies with n=0 adverse effects clearly related to this procedure.

Risk for bleeding, pneumothorax, and hypoxia from additional biopsies and lavage is monitored directly by trained pulmonary and critical care physicians. Direct or fluoroscopic visualization of the airway, the use of topical epinephrine to control bleeding, and other procedures occur in a devoted suite, hospital setting designed for emergency interventions, should they be necessary.

2. SURROGATE TISSUE

Five (5) specimen sets (sputum, buccal cells X 2 samples, exhaled breath, saliva X 2 samples, and blood) are proposed to serve as surrogate tissues to the lung biopsies and will be collected on consenting patients who are to undergo surgical lung resection, fiber optic bronchoscopy, CT screening for early detection of lung cancer, or related/unrelated controls not undergoing any of these procedures.

1. Peripheral blood samples

Purpose: Blood specimen is to be used in all groups for the tests for genetic susceptibility markers for lung disease

Procedure: A blood sample (30–40 cc/subject) will be collected at the same time as the clinically indicated specimens, voluntary blood donation or through an existing IV line if possible.

Risk: localized pain, redness, bruising (occasional) and infection (rare).

Benefit to subject: None.

2. Mouth cells

a) BRUSH EXFOLIATED BUCCAL SPECIMEN

Procedure: At least four (4) specimens in four separate vials will be obtained with a cell collecting brush such as a Cytobrush Plus ® by gently but thoroughly spinning the brush in place against the mucosal wall of each cheek with the cell collector for 5 seconds. Each cell collector will be put in a plastic tube with an appropriate RNA preservative solution and frozen at – 80 ° C.

Risk: Rare. Minimal discomfort, very rarely bleeding. Risk is minimized with gentle swabbing.

Benefit to subject: None.

b) MOUTHWASH ACQUIRED BUCCAL CELL:

Procedure: One (1) sample will be obtained by a swish and spit method using 15 ml of a common over-the-counter (OTC) mouthwash. Specimens will be collected in a sputum container and then transferred to a smaller plastic vial and frozen at – 80 ° C.

Risk: The over the counter mouthwash solution causes a tingling sensation that resolves quickly and rarely is a cause for discomfort. Possible after-taste of mouthwash resolves quickly.

Benefit to subject: None.

c) SALIVA COLLECTION

Purpose: Saliva may be collected twice; (a) one sample for cotinine assay. (b) Second sample for DNA adducts analysis.

Procedure: This will be accomplished by having subjects: (a) spit into special collection device and/or (b) chew on a cotton wool swab for 30 to 60 seconds.

Risk: Dislike the taste of cotton.

Benefit to subject: None.

3. Sputum

Procedure: Sputum will be collected either by spontaneous effort, or if necessary if subjects allow, by nebulizer induction (15cc hypertonic NS nebulization). Subjects will inhale approximately 15 ml (one tablespoon) of ultrasonically nebulized hypertonic saline over 10 minutes, then deep breath and cough directly into a sterile cup three times. Hypertonic saline (3%) is an osmotic airway secretion hydrating agent, and is routinely nebulized in clinical practice for the induction of sputum from those suspected of tuberculosis, and other conditions. In the research setting, the method has been used for carcinogenesis studies (Machida et al, 2006). The specimen will then be split to Saccomonos medium on wet ice and dry ice, and sent to the Spivack laboratory at AECOM.

Risk: The only known significant toxicity to sputum induction is cough, which is the desired outcome. Induced cough from nebulizer induced subsides without intervention. Hypoxia is extraordinary. Bronchospasm is rare but immediate treatment will be available if necessary.

Benefit to subject: None

4. Exhaled breath condensate

Purpose: For non-invasive sampling of the human lung, attempts to induce sputum yields none in >30-50% of symptomatic individuals, potentially precluding use of that lung-derived biospecimen for screening asymptomatic individuals. The investigator has considered exhaled breath markers as alternatives for risk assessment of former or current tobacco smokers. The availability of these easily collected specimens as "whole-lung" samplers is provocative for small molecules and volatiles, and now for larger molecule detection as well.

Background, exhaled breath: Chemical analysis of exhaled breath for the detection of oxidative stress and chronic inflammation, and for lung cancer, has been reported. We plan to evaluate the levels of volatile hydrocarbons in the gas phase of exhaled breath, and to collect exhaled breath condensate for the detection of markers for lipid peroxidation including hydrocarbons, aldehydes/ketones and glutathione, and for nucleic acids (DNA/RNA/metabolites for gene promoter methylation. Both of these breath sample types will be collected from study participants. Results from these marker assays will be compared with the other biomarkers measured in exfoliated buccal and bronchial cells, and lung epithelium.

Procedures: Collection of Exhaled Breath Fractions: Two fractions of exhaled breath will be obtained from each enrolled subject. The end-tidal volume will be sampled during the collection of exhaled breath condensate (EBC) using the commercially available disposable R tube (Respiratory Research Austin Texas). The EBC fraction is collected in the condenser portion (<0°C) of the R tube with sufficient liquid volume (>1 ml) obtained in 10 to 15 minutes of normal tidal breathing. The mouthpiece is separated from the cooling and collection vessel by a saliva trap, is at room temperature, and involves quiet, normal, tidal volume breathing. Nose clips are elective. The expiratory valve apparatus offers little resistance to exhalation. The team has used this handheld device in >700 subjects. The collection is to occur in the setting of an Einstein/Montefiore-based lung

cancer case- control setting (Spivack, PI), as well as in the context of the World Trade Center prospective cohort (Aldrich, PI), the Montefiore lung cancer CT screening program (Linda Haramati, PI) and the Bronx VAH (Robert Siegel, PI).

Risk: None apparent. This EBC technique has been published, commercialized, and otherwise used in widespread fashion for the last decade in a variety of research and clinical settings (see references). We have collected the sample from over 700 subjects under prior institution IRB- approved protocols without event.

Benefit to subject: None

3. QUESTIONNAIRES

Procedure: The subjects will be asked to complete a questionnaire regarding the amount he/she have smoked, diet, environmental exposures, medication and family history. This information is crucial to this study. The questionnaire will be administered by a research coordinator or self administered and takes about 10-15 minutes to complete. The questionnaire details the subjects' smoking history, environmental exposures to chemicals and materials, diet, personal and family history of cancers, medication history and for females, their menstrual status.

Risk: Minimal: Occasionally, the discussion smoking history or environmental contaminant exposure during the interview process may provoke anxiety.

Benefit to subject: None.

4. EXHALED CARBON MONOXIDE TESTING (Group 4 subjects only)

Purpose: Performed for biochemical confirmation of smoking status.

Procedure: The subject will be asked to take a deep breath, hold it for 15 seconds (or for as long as comfortably possible if the subject is unable to hold his/her breath for 15 seconds) and then exhale fully into the mouthpiece of the Bedfontpico+ Smokerlyzer Breath Carbon Monoxide (CO) Monitor. As per product specifications, subjects having ECO levels ≥ 7 ppm will be classified as current smokers.

Risk: The subject may feel uncomfortable while holding his/her breath for up to 15 seconds.

Benefit: None

TISSUE HANDLING

Each of the collected specimens will be placed in labeled vials containing an appropriate preservative, flash frozen within 15 minutes of collection, and placed in the tissue bank at -80°C (initial) to -170°C (Liquid N₂).

All lung biopsy tissue is batched, transported on dry ice and analyzed at the Spivack laboratories at the Price Center, AECOM. These specimens will be our referent lung tissues.

Extreme care will be taken when collecting all specimens so as not to contaminate the sample with extraneous DNA, and to preserve biological integrity.

RECRUITMENT

The prospective lung tissue-donating (3 digits, group 1 and 2) subjects anticipating lung resection surgery or bronchoscopy at AECOM affiliated institution will be contacted by telephone, letter, or in person. Research coordinator will see subjects for written consent, obtaining specimens and completing a questionnaire.

Recruitment of prospective non-lung-donating control subjects (4 digit subjects, individuals with no known lung disease; group 3) will be done by:

- a) Seeking volunteers through CCI-approved, community-focused advertisement or recruitment posters posted in AECOM-affiliated facilities.
- b) Seeking volunteers from adults who are undergoing phlebotomy for clinically indicated laboratory blood tests or for voluntary blood donations.
- c) Those undergoing CT screening at the Montefiore Lung cancer CT screening program.

Group 4 subjects will be recruited from the Montefiore Medical Center Infectious Diseases outpatient clinic during their scheduled visits. Research staff will see subjects for written consent, obtaining specimens and completing a questionnaire.

If subject agrees to participate:

- 1) Subject will be given complete and detailed information on study protocol and written informed consent will be obtained.
- 2) Permission to retain subject's specimens indefinitely in a tissue bank will be obtained. If this permission is not granted, the specimens will only be retained for the length of time currently approved by NYS law.
- 3) Permission for future contact/ follow up with patient will be obtained.
- 4) Information regarding the subject's smoking history, environmental exposures to chemicals and materials, diet, personal and family history of cancers, and medication history will be obtained.
- 5) Peripheral blood specimen will be obtained.
- 6) Mouth Cells will be obtained by both rinse and brush.
- 7) Saliva will be obtained by two collection methods.
- 8) Sputum will be obtained
- 9) Exhaled breath condensate will be obtained.
- 10) Lung tissue expressly for research purposes will be obtained during clinically-indicated, planned surgical or bronchoscopic procedures, by the subject's physician or surgeon, as described above.

Group 5 is a subset of Group 2 subjects who are undergoing clinical bronchoscopies and have consented to submit up to 15 brushes from their airways.

CONSENT

Consent is obtained in those undergoing clinically indicated surgery or bronchoscopy for interview (questionnaire), obtaining specimens, analysis and storage of tissue, receiving pathology reports on resected lung tissue, and future follow up. Consent is obtained in the control subjects for interview, obtaining specimens; analysis and storage of samples, and future follow up. The right to refuse to participate in any and all aspects of the study is explicit in the interview and consent process and forms. The protocol, informed consent and contact letters have been amended to comply with NYS Civil Rights Law 79-1, which concerns genetic testing on human subjects.

The informed consent states that:

- a) Specimens will be retained for the purpose of biologic and genetic testing focused on the susceptibility to lung cancer or other lung diseases by virtue of inhaled toxins, how the body metabolizes them and their biologic effects. The specific tests to be conducted on collected specimens are for genes that include inhaled foreign compound processing genes, certain cancer-associated and inflammation associated genes and other genes, proteins and biological markers associated with the metabolism of foreign substances (Tests including phase I and phase II metabolizing genes, oncogenes,

tumor suppressor genes and other genes, proteins and biological markers associated with foreign compound metabolism, carcinogenesis, inflammation and other processes and their effects on lung disease). GWAS/genome-wide discovery-compatible consent is granted.

- b) Subject gives permission for testing these specimens to Dr Spivack and his research associates only.
- c) Confidentiality is assured through coding of information and specimens collected by the following procedures. The investigator will be blinded to subject's identity by having all meaningful identifiers (SSN, MRN, DOB) removed prior to any information and/or specimens being sent to Dr Spivack and his research associates at the AECOM Price Center for genetic testing and storage. Results of any tests performed will not be linked back to the person and information relating the identity of any subject will not be disclosed.
- d) Specimens will be stored, without subject identifiers, in a tissue repository with limited access.
- e) Organizations that may have access to the research records are representatives from the Food and Drug Administration, the National Institutes of Health, NYSDOH, AECOM IRB, MMC IRB and AECOM GCRC if applicable.
- f) The subject gives permission so that the results of testing on his/her specimens may be included in future publications and that all identifying information will be kept confidential.
- g) In addition to the above, a separate signature line will be included for permission to hold all specimens collected for an indefinite period of time for the tests listed in the consent and for collaborative studies specified below as addenda
- h) Permission for future contact of the subject by the research team is granted.

SPECIMEN RETENTION

A separate section of the informed consent will be included to obtain the subject's approval for the investigator to retain their specimens for an indefinite period of time. This, according to New York State (NYS) law, as interpreted by the NYS Department of Health, requires separate consent. The subjects will be asked to sign their name and check whether they agree or disagree to have their specimens stored indefinitely.

If this separate consent is not signed, the specimens will only be retained for the maximum length of time approved (currently 60 days) per NYS regulations.

CONFIDENTIALTY

Confidentiality is maintained by the following blinding procedure:

1. Initially, each subject's questionnaire and every specimen collected will be coded with a unique study number as well as the subject's initials, medical record number, the institution where specimens were obtained and date of collection. This unique study number will ultimately be the only number available to the investigator in order to correlate all the various specimens with the subject's questionnaire and pathology report.
2. All subject identifiers (with the exception of the subject's study number) will be removed by the study coordinators prior to being sent to the investigator for genetic analysis and storage. Additionally, all pathology reports will be sent to the investigator only after the subject's identifiers are removed and replaced by the appropriate study number. These measures ensure that any information disclosing the identity of the person from whom the

sample is taken has been removed prior to investigator receiving the sample for genetic analysis.

3. The results of any subject's genetic testing will be known only to Dr Spivack and his research associates and, through the blinding process outlined above, will not be able to be linked to any specific individual. No information relating to the identity of any subject will be disclosed.
4. Subjects will have the right to refuse to donate any or all of the additional specimens. Organizations that may have access to the research records are representatives from the Food and Drug Administration, the National Institutes of Health, New York State Department of Health, Montefiore Medical Center-IRB, AECOM-CCI.

Certificate of Confidentiality clause has been added in all forms as follows:

“As a way to protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health, which is funding this study. If information from this study was requested or subpoenaed by government agencies or the courts, we will use the Certificate to attempt to legally refuse to provide it. This is rare – in only a few cases did researchers have to use the Certificate, and it was honored most of the time, but not every time. There are several kinds of situations that the Certificate does not apply. For example, we are still required to report child abuse and some diseases, and we must make data available to the government for a review or evaluation of our research. The Certificate does not prevent you or a member of your family from voluntarily sharing information. Similarly, if an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information”.

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GROUP 4 SUBJECTS

(Original description, sans ^MCpG distribution/power Figures)

Specific Aims:

Aim 1. To determine group EBC DNA methylation patterns by high resolution tagged bisulfite genomic sequencing of three tumor suppressor genes (*DAPK*, *RASSF1A*, *PAX5B*), according to smoking status (current, former, never), and lifelong dose (pack-years) in a sample of HIV-infected smokers.

Aim 2. To pilot the comparison of EBC DNA methylation from HIV infected individuals to that from uninfected individuals, collected in other projects funded by other mechanisms.

Aim 3. To examine the stability of EBC DNA methylation patterns over time in HIV-infected smokers.

Hypothesis:

Smoking alters exhaled DNA methylation of known carcinogenesis genes in HIV-infected individuals in a dose-dependent manner; this methylation is higher than HIV-uninfected individuals, and stable over time.

Background:

Highly active antiretroviral therapy (HAART) has transformed HIV infection into a chronic disease. Today's HIV care clinics service a middle-aged population with real prospects for long-term survival. As mortality from traditional HIV-related infections and neoplasms

decreases, a new set of “intersecting epidemics” has now emerged - HIV infection, cigarette smoking, tobacco-related malignancies and cardiopulmonary disease.^{1,2} Cigarette smoking is epidemic among persons living with HIV/AIDS, with cohort-documented cigarette smoking prevalences at 50-60%, nearly three times the 20.9% prevalence of the general adult population.³⁻⁸ The NIH has highlighted the need to confront the smoking problem in persons living with HIV/AIDS (PLWHAs).⁹ Studies in the HAART era consistently demonstrate a risk of primary lung cancer approximately triple that of the general population.¹⁰⁻¹³

Clinical features of lung cancer in PLWHAs. Lung cancer is now second only to non-Hodgkin’s lymphoma as a cause of cancer-related mortality in PLWHAs.¹⁴ In contrast to lung cancer in the general population, in PLWHAs it occurs at a younger age, typically in males who are heavy smokers and present with symptomatic, advanced disease.¹⁵ In general, the degree of immunosuppression is not severe, with mean CD4+ lymphocyte counts at presentation exceeding 200 cells/uL.^{14,15} The aggressive course of lung cancers in PLWHAs has been noted repeatedly, with a dismal one-year survival of 10%.¹⁵⁻¹⁹

Biologic features of lung cancer in PLWHAs. Impaired immunologic surveillance has been proposed as a causative factor in some AIDS-related malignancies although there is no clear correlation of lung cancer incidence with CD4+ lymphocyte count.¹³ And while the oncogenic viruses HPV, HCV, EBV, HHV-8, and HIV itself are highly prevalent among PLWHAs²⁰ careful studies have failed to consistently identify genomic material of these oncogenic viruses in the respective lung tumors.¹⁵ Suggestions of enhanced genetic instability (microsatellite change) may contribute to the incidence of lung cancers in HIV infection, as may the mutagenic nucleoside reverse transcriptase inhibitors, perhaps as co-carcinogens.^{15,21}

Key hurdles to human studies in lung carcinogenesis: A means to procure lung cell derivatives from large numbers of individuals by simple noninvasive means, would permit direct human studies of lung carcinogenesis. For non-invasive sampling of the lung, spontaneously-exfoliated cells in sputum are a potential source of lung epithelium, and other cells. However, attempts to induce sputum are unsuccessful in >20-50% of asymptomatic individuals^{22,23}. Alternatively, exhaled breath is readily provided²⁴, and exhaled DNA may be isolated from its condensate²⁵⁻²⁷. Our lab has confirmed the presence of DNA²⁸ in >40 subjects. Methylation pattern analysis suggests that EBC-DNA is not simply a contaminant from the oropharynx (not shown); further validation is being pursued under an NCI-R21 grant (Spivack).

High resolution measurement of exhaled DNA methylation at specific loci: Several high resolution methods have been developed to determine the methylation status of cytosine at any given CpGsite, including bisulfite genomic DNA sequencing (BGS), and MS-based MassArray®. For this proposal, we will employ our recent tagged primer adaptation (tBGS) that avoids DNA cloning²⁸. The single base resolution detail and comprehensive maps exceed that available from conventional assays. Application to exhaled breath condensate specimens (EBC) represents a novel approach; our submitted data represent a first report. The data presented in Figure 1 attests to the promise of this technique in distinguishing DNA profiles according to smoking backgrounds, and as a potential tool for the early diagnosis of lung cancer. For example, in the initial 38 non-HIV infected subjects, we found higher aggregate DNA methylation in the three gene promoters to both smoking status ($p=0.0030-0.0045$), and to lung cancer case-status ($p=0.000-0.0060$, Fig.1). Pilot lung cancer case-control discrimination yields area under the curve (AUC) for receiver operator curves (ROC-AUC=0.84-0.91, $p=0.0070-0.0005$, not shown²⁹). Exhaled Micro RNA studies are pending.

Research Design and Plan:

Study Design. Specific Aims 1 and 2 will be studied in a cross-sectional manner, enrolling a convenience sample of PLWHA smokers attending the Montefiore Medical Center (MMC)

Infectious Diseases (ID) Clinic. Specific Aim 3 will employ a prospective design, collecting two specimens over time from a subset of the overall study sample.

Study Setting. Study related clinical activities will occur in the Montefiore ID Clinic. The MMC ID Clinic is the largest individual HIV care site in New York State, and it provides comprehensive medical care to over 2600 PLWHAs. A research suite, equipped with private examining rooms and space for storage of research records is located one floor below the clinic. The HIV-infected patient population has a mean age of 47 years. Forty-five percent are female, 54% Latino/a, 40% African American/Caribbean, 4% White, non-Latino/a. The patients report various overlapping transmission categories: 51% heterosexual, 19% IDU, 14% same sex contact, and 14% unknown. Approximately 68% of patients have CDC-defined AIDS, and 75% are on HAART. Two-thirds of patients report having smoked a cigarette within the past week (B. Zingman, MD, personal communication). PLWHA smokers in the clinic consume a mean of 14 cigarettes per day, and have been smoking for a mean of 29 years. Forty-eight percent report concurrent intranasal or inhaled cocaine use, and 47% report concurrent marijuana use. The ID Clinic owns and maintains a modern exhaled carbon monoxide (eCO) monitor for biochemical confirmation of smoking status in ongoing smoking-related research projects.

Laboratory Resources. *Spivack lab:* A fully equipped laboratory (1,000 sq. ft.) set up for modern biochemistry, molecular genetics and cell biology within the Center for Genetic & Translational Medicine (CGTM), at the newly-constructed Price Center on the AECOM main campus. All equipment typical of a modern molecular biology and genetics laboratory. *Adjacent laboratory resources:* DNA sequencing core, equipped with multiple conventional dideoxy-capable capillary set-up (ABI 3130 or equivalent); the informatics and statistical resources of the AECOM Epigenomics Center (MFazzari) and BISR (TWang).

Subject Accrual. We plan to enroll 100 HIV-infected subjects over a period of six months. The research assistant will attend two clinic sessions weekly during this time, and will aim to recruit two new subjects of the 50 patient subjects seen at each clinic session. Numerous prior low-risk studies have successfully employed these strategies to meet comparable or larger accrual targets in the ID Clinic. For Specific Aim 3, the research assistant will maintain a log of enrolled subjects and identify those scheduled for clinic visits at least three months after enrollment. Virtually all clinic patients are scheduled for follow-up at least every three months. Subjects from the original cohort attending a follow-up visit at three or more months post-enrollment will be invited to complete a second study visit, until the follow-up cohort of 30 subjects is assembled, to address the issue of exhaled DNA methylation stability over time.

Study Visit Activities:

- a) *Clinical Questionnaire:* At point-of enrollment, participants will complete a previously validated questionnaire containing questions pertaining to socio-demographic characteristics, tobacco and other substance use, history of lung disease, as well as an additional module pertaining to HIV infection, opportunistic illnesses, and antiretroviral exposure. Participants will also undergo exhaled carbon monoxide testing using the BedfontpiCOSmokerlyzer at baseline in order to confirm smoking status.
- b) *Exhaled breath condensate collection (EBC):* Briefly, a disposable inner R-tube® (Respiratory Research, Charlottesville, VA) of polypropylene with one way valve, comes in contact with patients breath. There is additionally a reusable outer freezer-cooled cooling sleeve (-80°C) and insulating layer, The subject quietly breaths (at normal tidal volume with a sigh each minute) into the disposable inner tube by mouth, with nose clips for 15 minutes, while reading or engaging in another quiet activity. At the end of the session, the condensate specimen is sealed, and transported to the Spivack laboratory for DNA analysis.

- c) Saliva collection: Saliva may be collected twice. This will be accomplished by having subjects: (a) spit into special collection device and/or (b) chew on a cotton wool swab for 30 to 60 seconds.

Methylation data handling: The presence, partial presence, or absence of methylation at a CpG site is assessed by comparing bisulfite treated to untreated genomic DNA sequence by tBGS, using software sequence alignment, and verified at CpG sites by direct review of cycle sequence chromatogram tracings. The data spacially compresses to a single metric, percent of sites methylated (methylation “density”). Alternatively, another approach is to preserve spatial patterns across different CpG sites in a given gene promoter; regression of mean methylation rates in a given region can serve as group summary (Fig. 1).

Statistical analyses: We will employ multivariate modeling of individual *a priori* hypotheses to be tested. Principle analysis of the *main effects of smoking* (Aim 2) on EBC methylation density and spatial patterns, will be based on a linear regression with potential covariates (such as age, HIV infection, and underlying lung disease) included in the model. Principle analysis of the *main effects of HIV infection* (Aim 3) will consider potential covariates (age, underlying lung disease, smoking status). The comparison group will be that from an age- and smoking status frequency-matched cohort, from other Spivack laboratory projects. The EBC from these non-HIV infected individuals is being analyzed for the same markers by the same techniques, and is the source of pilot data (Fig. 1,2). For *measurement of methylation map stability* (Aim 3), we will use a repeated measures design. Corrections for multiple comparisons and measurements will be performed. False discovery approaches will be used. The Biostatistics Resource will be enlisted.

Power: This is a pilot discovery study. We will prioritize smoking and HIV infection as the primary, prioritized endpoints of interest. While we have no pilot EBC-DNA methylation variance data on those with HIV infection (n=110) versus those without HIV infection (n=75), if we assume similarities to data we have piloted in the non-HIV population we will have sufficient power for the analyses described.

Timeline: We completed accrual within the first six months (from January to July, 2009), The Spivack lab will analyze the EBC from the recruited ~100 HIV-infected individuals. The 75 non-HIV-infected individuals’ data (from a separate, NCI-funded project) will be available by that same time point. The team will then analyze the data using multivariate linear and regression analyses, for reporting purposes. A manuscript, and an NIH R01 application, will result.

Group 4-specific Literature Citations:

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GROUP 5 SUBJECTS

(Collecting extra bronchial brushes in a subset of Bronchoscopy cases)

Introduction: Using the same bronchial brush protocol as previously, we expect to get extra brushes for each tissue phenotype in a subset of 50 lung cancer (case) individuals undergoing bronchoscopy for clinical indications (e.g. diagnosis, airway therapeutics/palliation) . Three tissue phenotypes are of interest, and defined by the combination of white light (WB) and LIFE (fluorescent) bronchoscopy: (a) obvious visible endobronchial tumor tissue; (b) visible dysplastic tissue (by reflectance); and (c) visibly normal bronchial tissue (by reflectance). Laser induced fluorescent endoscopy has been FDA approved for detection of dysplasia for >5 years in the endobronchial epithelia, is innocuous, and prolongs under standard WB clinical procedures ~10-15 minutes. The procedure is performed through similar bronchoscope as standard white light bronchoscopy, except the light source is altered. The instrument is in clinical use in the MMC bronchoscopy suite (Dr. C Shah and Dr. A Sadoughi)).

The intent for this subset of patients is to get 3-5 brushes per tissue phenotype per subject. Thus, 9-15 brushes per case subject will be the intent. The protocol will be in use for appropriate bronchoscopy cases of Dr. C Shah and Dr. A Sadoughi, the interventional pulmonologist, as she has longstanding skills in LIFE examination, as well as advanced airway procedures (stents, lasers, cryotherapy, photocoagulation, etc.) and patency maintenance.

After the WB procedure for clinical purposes is completed, checking that the patient is tolerating that procedure well, we will exchange scopes to the LIFE bronchoscope. The LIFE bronchoscope will be advanced to an: (a) area of overt (WB+LIFE-confirmed) malignancy, and cytologically brush (abrade) the bronchial surface of that area with three to five separate brushes, each intended for a different set of assays (DNA, RNA, microRNA, metabolites, cytopathology) each requiring different buffers. The procedure will go to five brushes per area as long as patient and mucosa are tolerant. We will repeat the procedure, collecting three to five brushes for each airway tissue phenotype: (b) dysplasia represented by brown discoloration on LIFE bronchoscopy; and (c) normal endobronchium by WB and LIFE bronchoscopy consensus.

Procedure will be immediately stopped for significant bleeding, refractory cough, or any clinically apparent subject intolerance (hypoxia, sedation inadequacy/refractoriness, etc.) to the extra brush collection.

Incremental risk for 15 total brushes, versus current four collected, is for bleeding, cough, and prolongation of procedure under mild-moderate sedation, estimated as <0.1%, according to literature, in turn based on (i) risk of more advanced procedures (transbronchial biopsies, etc), and (ii) our extensive clinical and recent research experience.

USAMRMC Human Research Protection Office Continuing Review Submission Checklist

Protocol Title "Genetics of Lung Disease (Exhaled Breath DNA Methylation in Lung Carcinogenesis)"
Submitted By Dr. Simon D. Spivack, Albert Einstein College of Medicine of Yeshiva University, Bronx, NY
Supporting Proposal "Further Development of an Exhaled microRNA Biomarker of Lung Cancer Risk"
Submitted By Dr. Simon D. Spivack, Albert Einstein College of Medicine of Yeshiva University, Bronx, NY
Proposal/Study Number LC150738
Award Number W81XWH-16-1-0328
HSRRB Log Number A-19608.a

The following checklist is provided as guidance regarding the required documents and information to be included in the continuing review submission. Please ensure that applicable items are addressed in the continuing review report or attached in a separate document.

- Continuing review summary report that was submitted to your IRB.
- Local IRB approval letter with next expiration date.
- N/A If there was a lapse in approval of more than 1 day, explanation and confirmation that no study-related procedures occurred during the lapse.
- Current copy of protocol.
- Current consent form if applicable.
- Total number of subjects enrolled in the study.
- Substantive Amendment(s). Copies of amendment submission forms, amendment approval letters, and all revised and tracked documents, if a substantive amendment was approved by the IRB and not submitted to HRPO previously.

Note: The USAMRMC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution, change to the IRB, elimination or alteration of the consent process, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc), significant change in study design (i.e. would prompt additional scientific review) or a change that could potentially increase risks to subjects.

N/A Unanticipated problems involving risks to subjects or others (UPIRTSO). Copies of the event(s) description and documentation of IRB review if a UPIRTSO occurred and was not submitted to HRPO previously.

Note: UPIRTSOs are defined as problems/events that are:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the consent document; protocol-related documents, such as the IRB approved research protocol and informed and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility in the research); that the incident, experience, or outcome may have been caused by the procedures involved and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

N/A Documentation of suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the sponsor, or regulatory agencies.

Name of individual to contact with questions regarding this report DR. SIMON SPIVACK; DHRUV PATEL;
ADITI DESAI; DAWN BOWEN-JENKINS

dhruv.patel@einstein.edu; aditi.desai23@gmail.com;
simon.spivack@einstein.edu; bowen.jenkins@einstein.edu

Contact information (include email and phone number) #: 7186781040

Date (day month year) 01/18/2018

Progress Report (Version 3.1)

1.0 General Information

The version you are using is: August 2017 A

1.2 For all studies migrated from PATS or West Campus/paper:

Progress Reports may NOT be submitted before a Migration Completion Form has been approved by the IRB. If your Migration Completion Form has not been approved, this progress report will be rejected by the IRB.

Questions? Please contact iris-support@einstein.yu.edu.

1.3 Study Information

IRB #:

2007-407

Submission Reference #:

034775

Study Title:

Genetics of Lung Disease (Exhaled Breath DNA Methylation in Lung Carcinogenesis)

Principal Investigator:

Simon Spivack

1.4 Please click Save and Continue.

2.0 Will you be terminating this study?

2.1 Will you be terminating your research at this time?

Yes No

3.0 Progress Report Questions

3.1 Certificates of Confidentiality

Does this study receive funding from the NIH (either directly or through a subcontract)?

Yes No

Information about Certificates of Confidentiality for NIH-funded studies

On October 1, 2017 NIH updated its Certificates of Confidentiality (CoC) policy. Under this policy, CoCs will apply to ALL NIH-funded studies that collect identifiable data or biospecimens or generate human genomic data. All NIH-funded studies under this policy must meet the requirements described **here**.

Any NIH-funded studies that will consent subjects or are currently consenting subjects, must include the following language in their consent documents. *If this language is missing from your consent documents, you must submit an amendment to add this language.*

Certificate of Confidentiality

As a way to protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health, which is funding this study. If information from this study was requested or subpoenaed by government agencies or the courts, we will use the Certificate to attempt to legally refuse to provide it. This is rare – in only a few cases did researchers have to use the Certificate, and it was honored most of the time, but not every time. There are several kinds of situations that the Certificate does not apply. For example, we are still required to report child abuse and some diseases, and we must make data available to the government for a review or evaluation of our research. The Certificate does not prevent you or a member of your family from voluntarily sharing information. Similarly, if an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

3.2 Has any information appeared in the literature since the last progress report* of this protocol (especially as the findings relate to risks or benefits to the subject, or the significance of the research, or to the development of new treatment modalities)?

Yes No

If "Yes", describe below:

1-Non-invasive risk biomarkers for lung cancer: An exhaled microRNA panel interrogation and validation
W. Han, M. Shi, S. Keller, M. Aldabagh, S. Malik, J. Dobkin, D. Hosgood, C. Shah, S. Spivack
Albert Einstein College of Medicine/Bronx, NYC, USA.
2-Targeted DNA methylation and inactivation of endogenous genes using CRISPR-DNMT3a fusion protein
W. Han, A. Yan, M. Shi, Y. Peter, M. Levy, S. Spivack

**For studies where this is the first progress report, the "last progress report" refers to the new protocol application.*

3.3 Does the protocol have a Data Safety Monitoring Board (DSMB) or Data Safety Monitoring Committee (DSMC)?

Yes No

If "Yes," do you have a copy of the latest report or statement?

Yes No

You will be asked to attach it later in the submission form.

If you do not have a copy of the latest report, provide an explanation below:

3.4 Are there any preliminary findings?

Yes No

If "Yes," describe them below, especially noting any findings that would affect the risks or benefits to participants.

We are technically able to add case-control discriminant power by our first-pass exhaled microRNAs, though the incremental ROC is modest, around 5% so far. No findings affect risks to benefits to participants.


3.5 If you answered "Yes" to questions 1-3 above, could any of the new information, DSMB/DSMC report or preliminary findings affect the participants' willingness to continue in this protocol?

Yes No

3.6 Do you have any external audit reports?

Yes No

3.7 Upload IRB approval letters from external sites below. Only upload letters that have not already been submitted to the IRB.

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
1.0	161221 SIE-16-048 RDC Initial Approval and ACOS stmt	Approval Letter		Acknowledged		 67.40 KB

Only the following types of files may be uploaded into iRIS: .doc, .docx, .rtf, .txt, .pdf. The use of other file formats may delay IRB review and approval of your submission.

If any of the external sites do not have approval letters (e.g. the site has not been initiated, the site is permanently closed to enrollment), provide an explanation below:

4.0 COI Check Information

4.1 NOTE: THIS SUBMISSION WILL BE DENIED AND SENT BACK TO THE RESEARCHERS IF ANY INVESTIGATORS DO NOT HAVE CURRENT COI DISCLOSURES ON FILE (SEE #1 BELOW FOR DETAILS).

4.2 In order to ensure prompt review by the COI committee, you must complete the following steps:

4.3 1. Verify that the Principal Investigator and Additional Investigators (individuals listed in section 3.2.a) have current (filed within the past 6 months) COI disclosures on file. A list of individuals with COI disclosures on file can be accessed here (from YU/Einstein /Montefiore locations ONLY).

4.4 2. The IRB recommends that you send the following information by e-mail to all investigators who do not have a current COI disclosure on file:

**4.5 PI Name:
Protocol Title:**

Conflict of Interest (COI) disclosure forms are accessible via the COI web system. You have to be registered as a user – in the COI web system - in order to complete a Conflict of Interest disclosure form. The COI web system requires MMCAD username credentials for access.*

Please go directly to the COI web system log-in screen and request access to the COI web system. At this temporary link <https://eph.montefiore.org/COIFront/> you will be prompted to enter your MMCAD credentials. (Using the temporary link, it will be necessary to choose the options to bypass the security certificate warning.)*

Once reaching the main COI log-in page:

1- If you are new to the COI web system, the system will tell you it does not recognize you and will ask if you'd like to create a user profile. Agree. Your request will be reviewed and approved as soon as possible. You will receive an automated e-mail informing you of your ability to access the system once approved.

2- If you have completed a COI disclosure form in the past and the system tells you it does not recognize the MMCAD credentials you are using, please send an e-mail to COI@einstein.yu.edu stating you need your log-in credentials updated in the COI web system.

**For those without MMCAD credentials, please contact COI@einstein.yu.edu and include in the e-mail your full name, department, office /lab number, e-mail address, the purpose of your request (IRB submission, grant application, academic appointment, etc.), MMCAD username (if known), and the attached form completed. PLEASE DO NOT REQUEST A NEW MMCAD CREDENTIALS IF YOU HAVE ALREADY BEEN PROVIDED THEM. Contact COI@einstein.yu.edu.*

4.6 I understand that if any Key Personnel do NOT have a Conflict of Interest disclosure on file, the IRB application will NOT reach the IRB.

I have checked that the Principal Investigator and all Additional Investigators (individuals listed in section 3.2.a) have current electronic Conflict of Interest disclosures on file.

5.0 CITI Check Information

5.1 PRINT THESE INSTRUCTIONS SINCE YOU WILL NEED TO NAVIGATE AWAY FROM THIS FORM.

Click "Print Friendly" and select "HTML Form" and click OK.

5.2 Instructions for checking the education status for key personnel:

1. Open iRIS in a second browser such as IE, Chrome or Firefox.
2. Click on Study Assistant > My Studies
3. Click on the notepad icon next to your study to open the study.
4. Next to Navigation in the blue field above, click on "study mgmt."
5. Click on the Study Management tab (on the upper left, a little bit underneath the red IRB number).
6. Click on Study Summary/Profile.
7. Click on the head icon next to each study personnel (except those listed ONLY as study contacts). The CITI status is under Education History. The following courses qualify for the education check: Basic Course and Refresher Course and any course name with "Human" in the beginning. Effective January 1, 2015, Good Clinical Practice (GCP) training is required of all KP for studies involving drugs and/or devices. Effective January 1, 2017, GCP training is required for all KP on NIH-sponsored, NIH-defined clinical trials. For more information on GCP courses click here.
8. If the Education History only has expired courses, the Key Personnel will NOT pass the CITI check on iRIS. As a result, the IRB application will not be received by the IRB.

5.3 I understand that if any Key Personnel do NOT pass the CITI education check, the Progress Report will NOT reach the IRB and the IRB approval may expire.

I have checked the CITI status of all Key Personnel on this study.

6.0 Upload Data Safety Monitoring Committee/Board Report

6.1 Upload the DSMB/DSMC report below:

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
1.0	DATA SAFETY MONITORING REPORT	DSM Minutes /Charter		Acknowledged		 38.04 KB

Only the following types of files may be uploaded into iRIS: .doc, .docx, .rtf, .txt, .pdf. The use of other file formats may delay IRB review and approval of your submission.

7.0 Upload Adverse Event and Protocol Deviation Logs

7.1 Upload the Adverse Event and Protocol Deviation logs below:

Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
No Document(s) have been attached to this form.						

Only the following types of files may be uploaded into iRIS: .doc, .docx, .rtf, .txt, .pdf. The use of other file formats may delay IRB review and approval of your submission.

7.2 If there were no adverse events or deviations for the reporting period (and thus no logs), check one or both boxes below:

- I confirm that there are no AEs for this reporting period for this study.
- I confirm that there are no deviations for this reporting period for this study.

8.0 Protocols enrolling participants at sites under the jurisdiction of the Einstein IRB (including sites with an IIA or IAA)

8.1 Status

- Not initiated
- Enrollment ongoing
- Permanently closed to accrual, study participants still active or in follow up
- Permanently closed to accrual, data analysis only
- Study is terminated

8.2 Number of participants requested in the protocol application:

2000

If this number is not visible, follow these steps:

1. *Open another session of iRIS in a different web browser (i.e., Internet Explorer, Chrome, Firefox)*
2. *Study Assistant > My Studies > Click on the notepad next to this study*
3. *Click on Study Application (under Protocol Items on the left)*
4. *Click on the notepad*
5. *Click on "Section view of Application" tab*
6. *Click on "Accrual Information"*
7. *Refer to the response for question #3 on this page.*

To find the number of participants reported in previous progress reports, follow these steps:

1. *Open another session of iRIS in a different web browser (i.e., Internet Explorer, Chrome, Firefox)*
2. *Study Assistant > My Studies > Click on the notepad next to this study*
3. *Click on Progress Report (under Post-Approval Forms on the left)*
4. *Click on the notepad next to last year's progress report*
5. *Click on "Protocols enrolling under the jurisdiction of the Einstein IRB"*

8.3 Number of participants

If no participants have been enrolled or the protocol has not been initiated, enter the number 0 into the boxes below.

A. Number of participants enrolled* since last review**:

30

**Participants are enrolled when they sign the consent document.*

***For studies where this is the first progress report, the "last review" refers to the new protocol application.*

B. Number of participants who have withdrawn (voluntarily or by the PI) or who have been lost to follow-up since last review** :

0

Provide the reasons for the participant withdrawals:

C. Total number of participants enrolled* since project initiation:

786

The number in C must equal both of the following:

$C = D + E + F + G$

AND

$C = \text{this year's A} + \text{last review's C}$.

To find last review's see for Progress Reports submitted in iRIS:

1. Next to **Navigation** in the blue field above, click on "**Progress Report List.**" You have returned to

the Progress Report Page.

2. Click on the "notepad" next to your last review's Progress Report. Click on the Section labelled "Protocols enrolling under the jurisdiction of the Einstein IRB" and record the number.

3. Click on the iRIS **Back** button on the upper right.

4. Click on the "notepad" next to your current Progress Report. Click on the Section labelled "Protocols enrolling under the jurisdiction of the Einstein IRB".

If it does NOT, provide an explanation below:

D. Number of participants currently active on protocol:

779

E. Number of participants no longer active, but currently being followed:

0

F. Number of participants who have completed the protocol:

0

G. Number of participants who have withdrawn (voluntarily or by the PI) or who have been lost to follow-up since project initiation:

7

Does the total number of participants enrolled since project initiation exceed the number requested in the protocol application?

Yes No

If "Yes," provide an explanation below. An amendment may be required.

8.4 Non-English-speaking participants

Number of Spanish-speaking participants enrolled* since last review** with Spanish language consent document:

0

Number of participants speaking other languages enrolled* since last review** with non-English consent document (click on **Add a new row** to complete the table below):

Language	Number of Participants	Type of Consent	
No records have been added			

*Participants are enrolled when they sign the consent document.

**For studies where this is the first progress report, the "last review" refers to the new protocol application.

8.5 Complaints

Have there been any complaints about the protocol since it was last reviewed* by the IRB?

Yes No

*For studies where this is the first progress report, the "last reviewed" refers to the new protocol application.

If "Yes," list them below:

8.6 Suspensions at sites under Einstein's jurisdiction

Is the study suspended at any sites under Einstein's jurisdiction?

Yes No

If "Yes," who suspended the study?

If "Yes," which sites was it suspended at?

If "Yes," why was the study suspended?

9.0 Final Page

9.1 Congratulations! The Progress Report is complete. Click "Save and Continue" to send the report to the PI for signature.

If you have any additional comments that you would like to convey to the IRB staff, please enter them here:



Albert Einstein College of Medicine

Science at the heart of medicine

Institutional Review Board

Albert Einstein College of Medicine
FWA #00023382

Montefiore Medical Center
FWA #00002558

North Bronx Healthcare Network
FWA #00009807

Yeshiva University
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<http://www.einstein.yu.edu/irb>

Notification of Amendment Approval

Date: January 18, 2018

Principal Investigator: Simon Spivack

Study Title:	Genetics of Lung Disease (Exhaled Breath DNA Methylation in Lung Carcinogenesis)		
IRB #:	2007-407	Reference #:	037905
Amendment		Study	
Approval Date:	01/18/2018	Expiration Date:	11/07/2018

This amendment was reviewed and approved by expedited review under 45 CFR 46.110 and 21 CFR 56.110.

Approved Documents: To obtain a list of documents that were approved with this submission, follow these steps: Go to Study Assistant – My Studies and open the study – Click on Submissions History – Go to Completed Submissions – Locate this submission and click on the Details button to view a list of submitted documents and their outcomes.

For a list of all currently approved documents, follow these steps: Go to Study Assistant – My Studies and open the study – Click on Informed Consent to obtain a list of approved consent documents and Other Study Documents for a list of other approved documents.

Reminders

All changes to a study must receive IRB approval before they are implemented. The only exception to the requirement for prior IRB review and approval is when the changes are necessary to eliminate apparent immediate hazards to the subject (45 CFR 46.103(b)(4), 21 CFR 56.108(a)). In such cases, report the actions taken as a reportable event.

Reportable Events must be reported to the IRB in compliance with the Einstein IRB policy.

Expiration Notice: IRB approval for this study is limited to the period specified above. In order to gain re-approval, you must submit a Progress Report prior to the expiration of the study. When the research is completed, submit a final Progress Report. The iRIS system will generate an email notification 60 days prior to the expiration of this study's approval. However, it is your responsibility to ensure that a Progress Report has been submitted by the required time.

**Institutional Review Board
Bronx VA Medical Center
Research & Development Program (151)**

130 West Kingsbridge Road • Bronx, NY 10468 • 718-741-4228 • Fax: 718-741-3937

IRB APPROVAL - Continuing Review

Date: September 20, 2017

From: Juan C. Bandres, M.D., Ph.D., Chairperson 

Investigator: Robert E. Siegel, M.D.

Protocol: Further Development of an Exhaled microRNA Biomarker of Lung Cancer Risk

ID: 01711 Prom#: N/A Protocol#: SIE-16-048

The following items were reviewed and approved at the 09/07/2017 meeting:

- Abstract (Protocol Summary) (08/14/2017)
- Annual Adverse Event Report Form (08/14/2017)
- Annual Enrollment Form (08/14/2017)
- Budget Page (08/14/2017)
- Consent Form - clean (08/14/2017)
- Continuing Review (08/14/2017)
- Financial Disclosure Form - Margapuri - signed (09/20/2017)
- Lay Research Summary (08/14/2017)
- Personnel Record (08/14/2017)
- PI Annual Research Protocol Safety Update (08/14/2017)
- Progress Report (08/14/2017)
- Research Financial Conflict of Interest Statement (08/14/2017)
- Research Protocol (08/14/2017)
- Research Protocol Safety Survey-form 10-0398 (08/14/2017)
- Signature Page(s) (08/14/2017)
- Training (08/14/2017)
- Data Management Access Plan (08/14/2017)

The following additional items were received to address stipulations and are now approved:

- Financial Disclosure Form (08/14/2017)
- Response to Contingent Approval (09/20/2017)

Approval is granted for a period of 12 months and will expire on 09/06/2018. Your Continuing Review is scheduled for 07/05/2018, and the requirements are attached.

The protocol was determined to have the following level of risk:

Minimal risk

The following was resolved:

**Please submit the SIGNED FCOI form for Dr. Margapuri. The document is not signed.
CPRS flagging not required.**

Approval by each of the following is required prior to study continuation:
Institutional Review Board

Approval for study continuation is contingent upon your compliance with the requirements of the Research Service for the conduct of studies involving human subjects.



JAMES J. PETERS VA MEDICAL CENTER
130 West Kingsbridge Road
Bronx, New York 10468


Research & Development Program
ACOS Functional Statement

Date: September 30, 2017
From: Mary Sano, Ph.D.
Investigator: Siegel, Robert E., M.D.
Protocol: [SIE-16-048] Further Development of an Exhaled microRNA
Biomarker of Lung Cancer Risk
MIRB ID: 01711

This protocol has received continuing approval from all applicable Research & Development subcommittees. This is a notification to the investigator from the ACOS for R&D that this research can be continued.

FUNCTIONAL STATEMENT:

The PI/Co-PI is responsible for all aspects of this research consistent with information in this application, including supervising all staff associated with this project, insuring that all procedures are conducted by appropriately credentialed personnel, and securing all needed resources. The PI/Co-PI will be responsible for the integrity of the study, including data collection, data analysis, interpretation of results, and reporting of results.



Mary Sano, PhD, ACOS/R&D

10-10-17

DATE

Clinical Research Protocol: **GENETICS OF LUNG DISEASE**

Principal Investigator: **Simon Spivack, MD, MPH**

CCI#: **2007-407**

Locations/ Sites: Albert Einstein College of Medicine, Weiler Hospital and Moses Division of Montefiore Medical Center

Proposed number of subjects to enroll: 2000

Funding: National Institute of Health

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INTRODUCTION

This research study is a lung cancer case *versus* control (no lung cancer) comparison evaluating four issues.

- 1) To identify specific molecular events common to individuals with lung cancer and other lung diseases.
- 2) The degree to which the molecular genetic events of human lung carcinogenesis and other lung disease may parallel genetic events found in more easily accessed surrogate tissues, such as sputum, saliva, buccal cells, exhaled breath, and blood.
- 3) To identify markers of disease risk or prognosis for lung cancer and other lung disease.
- 4) To determine group EBC DNA methylation Patterns by high resolution tagged bisulfate genomic sequencing of three tumor suppressor genes (DAPK, RASSF1A, PAX5B), according to smoking status (current, former, never), and lifelong dose (pack years) in a sample of HIV-infected smokers.

These four goals anticipate attempts at molecular screening strategies for early detection of lung cancer, and other lung diseases.

PURPOSE

This research study is designed to explore pathways, genes and molecules that may be responsible for the susceptibility and/or development of lung disease in anticipation of establishing molecular screening strategies for the early detection of lung diseases, including cancer.

This research will attempt to establish a relationship between the molecular changes that occur in cells from the mouth, saliva, exhaled breath and blood as they relate to the development of lung disease. If this relationship can be proven, it may be possible in the future to test for certain lung diseases with a simple laboratory test. Dr. Simon Spivack, the principal investigator, is conducting a research investigation to determine whether the activity of certain genes and proteins in the lung and other tissues increases with exposure to cigarette smoke or other environmental hazards. This increased activity might impact the development of lung cancer and other diseases. Genes instruct proteins to control and direct many activities of cells in the human body. The genes of interest to this investigation include inhaled foreign compound- processing genes, certain cancer-associated and inflammation associated genes, and other genes, proteins and biological markers associated with the metabolism of foreign substances. The activity of genes and proteins found in the lung are thought to parallel that detected in blood, saliva, exhaled breath condensate (moisture) and mouth cells. This is unproven. Additionally, the relationship of these genes' activity to lung disease remains unproven.

The following is a list of genes for which DNA methylation, gene expression, or other alterations are currently being studied or is planned for study:

Ahr, ARNT, Nrf1-2, AP1, SP1, ERalpha, ERbeta, CYP1A1, CYP1B1, CYP2A13, CYP3A4, CYP3A5, GSTM3, GSTP1, GSTT1, SULT1-4, NQO1, CAT, GPx, GLCLC, SOD1, MRP1-10, BCRP, OGG, XRCC1- 4, ERCC1-4, NBS1, XPC, XPD, XPF, UNG1-2, MUG1-2, TDG, MBD1-4, MPG, MYH, NTH1-2, p53, kRas, p21, RASSF1A, PAX5B, CDH1, MGMT, p16 and other carcinogen and oxidant metabolism, DNA repair, cell cycle and other relevant carcinogenesis and inflammation related genes.

Selected lung specimens will also be shared with collaborating laboratories, for the purposes of: (a) tumor heterotransplantation into animals to test novel therapeutics and biomarkers; (b) testing for progenitor/stem cells in lung cancer; (c) other purposes by future collaboration.

- (a) The understanding of the molecular determinants of lung cancer development has evolved significantly over last several years. Several molecular markers have helped clinicians and scientist better understand and treat different subtypes on lung cancer. With the advent of many new chemotherapies and targeted therapies, it is becoming of paramount importance to understand the molecular changes in the individual tumor and develop effective targeted therapies.

One way to achieve this insight for personalized medicine, and improved chemotherapy, is through the heterotransplant model, where a small fragment of human tumor is implanted in nude mice. This allows investigators to study a variety of different chemotherapies and targeted therapies and to identify markers that will determine response to individual treatments. This type of approach has been well studied with traditional chemotherapies and has a very high correlation with clinical response rate. The heterotransplant platform give us a unique platform to further understand the molecular origins of lung cancer and will enable us to test the use of these as biomarkers to determine the response to new emerging targeted therapies. This will be done in collaboration with our co-investigators Dr. Piperdi and Dr. Perez-Soler from department of medical oncology.

- (b) Another type of study, to understand the role of stem cells in carcinogenesis, and tumor biology, involves determining the presence and behavior of stem cells. These are “outgrown” from small samples of the already surgically removed lung tissue. The cells’ behavior has implications for anticancer strategies. They are grown over generations, donor identity is not known to investigators, and therefore no linkage to identity is available. This aspect of the study will be done in collaboration with Dr. Yakov Peter of Yeshiva University.

SELECTION OF PATIENT POPULATION

- Group 1: Patients at least 21 years of age that have been seen and evaluated by a pulmonologist and are scheduled to undergo elective surgical lung biopsy or surgical resection for diagnostic/therapeutic purposes. (3 digit subjects)
- Group 2: Patients at least 21 years of age that have been seen and evaluated by a pulmonologist and are scheduled to undergo elective bronchoscopy for diagnostic purpose. (3 digit subjects)
- Group 3a: Subjects at least 21 years of age that have no known diagnosis of lung cancer will be enrolled as a control group. These subjects do not donate lung tissue itself, but do donate non-invasively-collected surrogates (blood, saliva, exhaled breath condensate, and mouth/buccal cells. (4 digit subjects)
- Group 3b: Subjects at least 21 years of age who are undergoing short term (nearly 3 months) follow up CT scan for a nodule/mass detected on initial/annual CT scan screening for lung cancer, will be enrolled as another control group. These subjects do not donate lung tissue itself, but do donate non-invasively collected surrogates (blood, saliva, exhaled breath condensates and mouth/buccal cells. (4 digit subjects).

Group 4: Subjects at least 21 years old with known HIV positive status. This group will donate exhaled breath condensate on two separate visits, complete a questionnaire, provide saliva and undergo exhaled carbon monoxide testing.

Group 5: Patients at least 21 years of age that have been seen and evaluated by a pulmonologist and are scheduled to undergo elective bronchoscopy for diagnostic purposes. This is a subset of group 2 with subjects consenting for more than 4 bronch brushes up to a maximum of 15 (3 digit subjects).

INCLUSION/EXCLUSION

Inclusion Criteria:

- Age: minimum age of 21 years
- Gender: Male and Female adults
- Ethnicity: All ethnic groups and races.
- Subjects undergoing bronchoscopy for diagnostic purposes or therapy.
- Subjects without a known diagnosis of lung cancer who are not scheduled for lung tissue collection procedures.

Addition Inclusion Requirements for Group 4 only: Immunologically or virologically confirmed HIV infection.

Exclusion Criteria:

No invasive research specimens (BAL/biopsy) will be obtained from bronchoscopy subjects with evidence of bleeding diathesis or known coagulopathy precluding clinically-indicated biopsy (e.g. INR>1.3, PTTr>1.3), thrombocytopenia <50k, uremia with serum creatinine >3.0, unstable angina, recent myocardial infarction (within 3 months), uncontrolled congestive heart failure or severe pulmonary hypertension (mean PAP>75 mmHg).

DISCONTINUATION

Subject or Attending Physician request that the patient be withdrawn from the study.

DATA SAFETY MONITORING PLAN

Two Pulmonary Medicine clinicians, not associated with the protocol, will monitor for adverse events, and study subject concerns. Neither is a collaborator/consultant/advisor, nor has a direct interest in the protocol. The committee will include:

1. **William N. Rom, MD, MPH**
Division Chief, Pulmonary & Critical Care Medicine, NYU Medical Center
2. **Timothy Harkin, MD**
Interventional Bronchoscopy Service
Pulmonary & Critical Care Medicine, Mt. Sinai Medical Center, New York City.

The committee shall meet prior to enrolling research participants. They will be informed of minor adverse events on a regular (q 6- month) basis, and of more serious adverse events when they occur.

SOURCES OF RESEARCH MATERIAL

1. **LUNG TISSUE** (described in detail in nih grant proposal)

1) Surgical lung harvest

Procedure: Lung resection specimens, which are not needed for clinical/pathologic diagnosis and which are normally discarded, will serve as the main source of surgical lung tissue.

One specimen obtained will be cancer/involved (tumor) or benign/involved (if non-cancer such as granulomas, fibrosis, etc.) tissue, and the other will be a non-cancer (non-tumor/non-involved, adjacent) specimen. Both of these two specimens will be placed in labeled vials containing an appropriate preservative, flash frozen within 15 minutes of surgical ligation, and placed at -70°C in the tissue bank at AECOM, for ultimate storage in the Spivack laboratory liquid N₂ tissue repository. However, selected lung specimens will be shared with collaborating laboratories, as described above, for the purposes of: (a) tumor heterotransplantation into animals to test novel therapeutics and biomarkers; (b) testing for progenitor/stem cells in lung cancer; (c) other purposes by future collaboration.

Risk: None. Surgical risk is unaffected by the study, as no alterations of the surgical procedure, nor additional tissue, is taken for research purposes. Physical risk is none incremental to that inherent to post-operative recovery. Inconvenience of an interview and surrogate tissue collection is the risk associated with the study itself.

Benefit to subject: None.

2) Bronchoscopy

Endobronchial biopsies (EBBx) (Consenting subjects undergoing fiber optic Bronchoscopy)

Purpose: To study the gene expression and epigenetic features of putative lung cancer risk genes in uninvolved bronchial mucosal tissue, as opposed to whole lung, in those with malignant and nonmalignant lung disease. This is best accessed by endobronchial brush or biopsy.

Procedure: All eligible consenting adults undergoing elective, non-emergent, non-ICU bronchoscopy at AECOM associated institutions would have four additional endobronchial biopsies performed under direct visual guidance, of visually non-involved areas of the proximal bronchial tree (2nd - 4th order bronchi). These four endobronchial bronchoscopic biopsies (which are in addition to, and taken after, any endobronchial specimens obtained by the pulmonologists for clinical purposes) will be taken as follows: (a) One of the specimens obtained will be from visually apparent cancer (tumor) tissue; and (b) The other three will be from non-cancer (non-tumor) airways. Several of the bronchoscopic lung biopsies from non-tumor tissue may be collected using a bronchoscopic brush. This brushed epithelium method of specimen collection has less associated risk to subjects than does endobronchial tissue forceps biopsy, and much less than transbronchial biopsy. Potential complications, where publications do exist, are described below.

Risk: Common: *Prolonged procedure*. Time added for extra brushing is about 1 minute per brush or 2 minutes for forceps, x 4 specimens= 4-8 minutes which should not affect duration of anesthesia (which is topical+parenteral conscious sedation).

Rare: *Bleeding*: (reported on a per procedure basis, not reported on a "per bite" basis). Minimal attributable incremental risk for bleeding associated with the fifth through eight endobronchial biopsy (not reported as incrementally risky in literature or our experience.) There is less physical risk to subjects who have the bronchoscopic brushing, which is not well estimated in literature. Bleeding complications are not typically listed specific to endobronchial biopsy itself, and certainly not specific to endobronchial brush specimens. A March 2008 review of literature update reveals no additional studies that breakdown that risk since the last search several years ago. In one study (Dransfield, 2003), the overall complication rate in a high-risk lung transplant population from conventional bronchoscopy included those procedures entailing endobronchial forceps (EBBx) and transbronchial forceps (TBBx) biopsies; a rate of 0.14% for major bleeding, and 0.28% for minor bleeding was reported. In another study, 17 total endobronchial forceps biopsy-induced bleeding episodes per 3096 bronchoscopy procedures with any type of biopsy (TBBx or EBBx) = 0.54%. EBBx termed "less likely to cause significant bleeding" than

TBBx so EBBx bleeding rate is likely less than 0.54% per multiple-biopsy procedure. For example, other authors report TBBx bleeding rate is 2.8% in TBBxl (not EBBx) biopsies (Pue 1995, HernandezBlasco LH, 1991). (3 of the 3096 bronchoscopic procedures were marked by "profuse bleeding", requiring nonsurgical interventions such as intratracheal instillation of topical epinephrine, or bronchoscope tamponade of the area (0.1%). The other 14 were minor or moderate, and resolved spontaneously within minutes. Risk factors for TBBx - and/or EBBx - induced bleeding are controversial, (Cordasco EM et al. Chest 1991) but may include clinical history of bleeding with invasive procedures, thrombocytopenia, coagulopathy, uremia, pulmonary hypertension, malignancy (remote or chest), and immunocompromised status.

Pneumothorax: (reported on a per procedure basis, not reported on a "per bite" basis) Not reported specifically for endobronchial forceps (EBBx) biopsy, and not reported for endobronchial brush (cytologic) sampling. The rates for EBBx under direct visual guidance are expected to be much less than the 0.3-0.7% rate that are estimated from those for TBBx (a much higher risk, fluoroscopically-guided procedure, for pneumothorax), the rates have ranged from 0.7 – 5.5% in larger series for TBBx. Collapsed lung from the extra bronchial samples procured for research (inferred as less than 0.30%) could result in the need to reinflate the lung, with a surgically-placed chest tube, over approximately a three-day admission to the hospital. There could be pain or discomfort associated with this rare event. We have now employed these research EBBx brushings in >200 clinical bronchoscopies, with n=0 adverse effects clearly related to this research procedure.

Benefit to subject: None.

Bronchoalveolar lavage (BAL)

Purpose: The procedure is designed to obtain (diluted) bronchiolar and alveolar lining fluid to detect DNA modification such as CpG methylation, for the purpose of determining the anatomic airway origin (pharynx versus major bronchi, versus bronchiole/alveoli) of exhaled DNA.

Procedure: Bronchoalveolar lavage is "piggy-backed" on clinically indicated bronchoscopies. This is incremental to bronchoscopy itself, and is a minimally invasive diagnostic technique involving the suffusion of up to five 20 cc aliquots of sterile saline into the mid-distal airways by wedging the bronchoscope and immediately retrieving that saline sampling of the distal bronchoalveolar tree. For consenting subjects having bronchoscopy for clinical indications, bronchoalveolar lavage (BAL) for research purpose will be performed after any clinically indicated biopsies.

Risk: Minimal. BAL is a routine clinical procedure, employed at >50% of all bronchoscopies, and does not result in any complications in approximately 95% of patients. Of the remaining ~5%, most complications are minimal and include transient (seconds-minutes) decrease in baseline *PaO2*, transient fever (2%), cough (~1%), transient chills (<1%), bronchospasm (<1%). Life threatening complications occur very rarely, estimated at <0.01%.

Benefit to subject: None

Overall, pneumothorax from BAL or endobronchial biopsy alone is rare. One clinical study in hematologic malignancy subjects showed no events in 45 subjects undergoing BAL alone (Mulabecirovic, 2004). Another study of research subjects undergoing endobronchial biopsy (n=98) or endobronchial biopsy combined with BAL (n=68) showed one pneumothorax in a subject with severe emphysema (Hattotuwa, 2002). In a clinical study of ~1300 children undergoing bronchoscopy outside of the intensive care unit for clinical indications, one pneumothorax requiring a chest tube insertion was noted in a child with bronchiectasis

undergoing endobronchial biopsy. Other electronically available studies in the last 12 years do not allow one to extract a pneumothorax rate specific to these three non-transbronchial biopsy procedures (Bronchoscopy, Endobronchial biopsy, and Bronchoalveolar Lavage (BAL)).

We have now employed these research BAL procedures in >200 clinical bronchoscopies with n=0 adverse effects clearly related to this procedure.

Risk for bleeding, pneumothorax, and hypoxia from additional biopsies and lavage is monitored directly by trained pulmonary and critical care physicians. Direct or fluoroscopic visualization of the airway, the use of topical epinephrine to control bleeding, and other procedures occur in a devoted suite, hospital setting designed for emergency interventions, should they be necessary.

2. SURROGATE TISSUE

Five (5) specimen sets (sputum, buccal cells X 2 samples, exhaled breath, saliva X 2 samples, and blood) are proposed to serve as surrogate tissues to the lung biopsies and will be collected on consenting patients who are to undergo surgical lung resection, fiber optic bronchoscopy, CT screening for early detection of lung cancer, or related/unrelated controls not undergoing any of these procedures.

1. Peripheral blood samples

Purpose: Blood specimen is to be used in all groups for the tests for genetic susceptibility markers for lung disease

Procedure: A blood sample (30–40 cc/subject) will be collected at the same time as the clinically indicated specimens, voluntary blood donation or through an existing IV line if possible.

Risk: localized pain, redness, bruising (occasional) and infection (rare).

Benefit to subject: None.

2. Mouth cells

a) BRUSH EXFOLIATED BUCCAL SPECIMEN

Procedure: At least four (4) specimens in four separate vials will be obtained with a cell collecting brush such as a Cytobrush Plus ® by gently but thoroughly spinning the brush in place against the mucosal wall of each cheek with the cell collector for 5 seconds. Each cell collector will be put in a plastic tube with an appropriate RNA preservative solution and frozen at – 80 ° C.

Risk: Rare. Minimal discomfort, very rarely bleeding. Risk is minimized with gentle swabbing.

Benefit to subject: None.

b) MOUTHWASH ACQUIRED BUCCAL CELL:

Procedure: One (1) sample will be obtained by a swish and spit method using 15 ml of a common over-the-counter (OTC) mouthwash. Specimens will be collected in a sputum container and then transferred to a smaller plastic vial and frozen at – 80 ° C.

Risk: The over the counter mouthwash solution causes a tingling sensation that resolves quickly and rarely is a cause for discomfort. Possible after-taste of mouthwash resolves quickly.

Benefit to subject: None.

c) SALIVA COLLECTION

Purpose: Saliva may be collected twice; (a) one sample for cotinine assay. (b) Second sample for DNA adducts analysis.

Procedure: This will be accomplished by having subjects: (a) spit into special collection device and/or (b) chew on a cotton wool swab for 30 to 60 seconds.

Risk: Dislike the taste of cotton.

Benefit to subject: None.

3. Sputum

Procedure: Sputum will be collected either by spontaneous effort, or if necessary if subjects allow, by nebulizer induction (15cc hypertonic NS nebulization). Subjects will inhale approximately 15 ml (one tablespoon) of ultrasonically nebulized hypertonic saline over 10 minutes, then deep breath and cough directly into a sterile cup three times. Hypertonic saline (3%) is an osmotic airway secretion hydrating agent, and is routinely nebulized in clinical practice for the induction of sputum from those suspected of tuberculosis, and other conditions. In the research setting, the method has been used for carcinogenesis studies (Machida et al, 2006). The specimen will then be split to Saccomonos medium on wet ice and dry ice, and sent to the Spivack laboratory at AECOM.

Risk: The only known significant toxicity to sputum induction is cough, which is the desired outcome. Induced cough from nebulizer induced subsides without intervention. Hypoxia is extraordinary. Bronchospasm is rare but immediate treatment will be available if necessary.

Benefit to subject: None

4. Exhaled breath condensate

Purpose: For non-invasive sampling of the human lung, attempts to induce sputum yields none in >30-50% of symptomatic individuals, potentially precluding use of that lung-derived biospecimen for screening asymptomatic individuals. The investigator has considered exhaled breath markers as alternatives for risk assessment of former or current tobacco smokers. The availability of these easily collected specimens as "whole-lung" samplers is provocative for small molecules and volatiles, and now for larger molecule detection as well.

Background, exhaled breath: Chemical analysis of exhaled breath for the detection of oxidative stress and chronic inflammation, and for lung cancer, has been reported. We plan to evaluate the levels of volatile hydrocarbons in the gas phase of exhaled breath, and to collect exhaled breath condensate for the detection of markers for lipid peroxidation including hydrocarbons, aldehydes/ketones and glutathione, and for nucleic acids (DNA/RNA/metabolites for gene promoter methylation. Both of these breath sample types will be collected from study participants. Results from these marker assays will be compared with the other biomarkers measured in exfoliated buccal and bronchial cells, and lung epithelium.

Procedures: Collection of Exhaled Breath Fractions: Two fractions of exhaled breath will be obtained from each enrolled subject. The end-tidal volume will be sampled during the collection of exhaled breath condensate (EBC) using the commercially available disposable R tube (Respiratory Research Austin Texas). The EBC fraction is collected in the condenser portion (<0°C) of the R tube with sufficient liquid volume (>1 ml) obtained in 10 to 15 minutes of normal tidal breathing. The mouthpiece is separated from the cooling and collection vessel by a saliva trap, is at room temperature, and involves quiet, normal, tidal volume breathing. Nose clips are elective. The expiratory valve apparatus offers little resistance to exhalation. The team has used this handheld device in >700 subjects. The collection is to occur in the setting of an Einstein/Montefiore-based lung

cancer case- control setting (Spivack, PI), as well as in the context of the World Trade Center prospective cohort (Aldrich, PI), the Montefiore lung cancer CT screening program (Linda Haramati, PI) and the Bronx VAH (Robert Siegel, PI).

Risk: None apparent. This EBC technique has been published, commercialized, and otherwise used in widespread fashion for the last decade in a variety of research and clinical settings (see references). We have collected the sample from over 700 subjects under prior institution IRB- approved protocols without event.

Benefit to subject: None

3. QUESTIONNAIRES

Procedure: The subjects will be asked to complete a questionnaire regarding the amount he/she have smoked, diet, environmental exposures, medication and family history. This information is crucial to this study. The questionnaire will be administered by a research coordinator or self administered and takes about 10-15 minutes to complete. The questionnaire details the subjects' smoking history, environmental exposures to chemicals and materials, diet, personal and family history of cancers, medication history and for females, their menstrual status.

Risk: Minimal: Occasionally, the discussion smoking history or environmental contaminant exposure during the interview process may provoke anxiety.

Benefit to subject: None.

4. EXHALED CARBON MONOXIDE TESTING (Group 4 subjects only)

Purpose: Performed for biochemical confirmation of smoking status.

Procedure: The subject will be asked to take a deep breath, hold it for 15 seconds (or for as long as comfortably possible if the subject is unable to hold his/her breath for 15 seconds) and then exhale fully into the mouthpiece of the Bedfontpico+ Smokerlyzer Breath Carbon Monoxide (CO) Monitor. As per product specifications, subjects having ECO levels ≥ 7 ppm will be classified as current smokers.

Risk: The subject may feel uncomfortable while holding his/her breath for up to 15 seconds.

Benefit: None

TISSUE HANDLING

Each of the collected specimens will be placed in labeled vials containing an appropriate preservative, flash frozen within 15 minutes of collection, and placed in the tissue bank at -80°C (initial) to -170°C (Liquid N₂).

All lung biopsy tissue is batched, transported on dry ice and analyzed at the Spivack laboratories at the Price Center, AECOM. These specimens will be our referent lung tissues.

Extreme care will be taken when collecting all specimens so as not to contaminate the sample with extraneous DNA, and to preserve biological integrity.

RECRUITMENT

The prospective lung tissue-donating (3 digits, group 1 and 2) subjects anticipating lung resection surgery or bronchoscopy at AECOM affiliated institution will be contacted by telephone, letter, or in person. Research coordinator will see subjects for written consent, obtaining specimens and completing a questionnaire.

Recruitment of prospective non-lung-donating control subjects (4 digit subjects, individuals with no known lung disease; group 3) will be done by:

- a) Seeking volunteers through CCI-approved, community-focused advertisement or recruitment posters posted in AECOM-affiliated facilities.
- b) Seeking volunteers from adults who are undergoing phlebotomy for clinically indicated laboratory blood tests or for voluntary blood donations.
- c) Those undergoing CT screening at the Montefiore Lung cancer CT screening program.

Group 4 subjects will be recruited from the Montefiore Medical Center Infectious Diseases outpatient clinic during their scheduled visits. Research staff will see subjects for written consent, obtaining specimens and completing a questionnaire.

If subject agrees to participate:

- 1) Subject will be given complete and detailed information on study protocol and written informed consent will be obtained.
- 2) Permission to retain subject's specimens indefinitely in a tissue bank will be obtained. If this permission is not granted, the specimens will only be retained for the length of time currently approved by NYS law.
- 3) Permission for future contact/ follow up with patient will be obtained.
- 4) Information regarding the subject's smoking history, environmental exposures to chemicals and materials, diet, personal and family history of cancers, and medication history will be obtained.
- 5) Peripheral blood specimen will be obtained.
- 6) Mouth Cells will be obtained by both rinse and brush.
- 7) Saliva will be obtained by two collection methods.
- 8) Sputum will be obtained
- 9) Exhaled breath condensate will be obtained.
- 10) Lung tissue expressly for research purposes will be obtained during clinically-indicated, planned surgical or bronchoscopic procedures, by the subject's physician or surgeon, as described above.

Group 5 is a subset of Group 2 subjects who are undergoing clinical bronchoscopies and have consented to submit up to 15 brushes from their airways.

CONSENT

Consent is obtained in those undergoing clinically indicated surgery or bronchoscopy for interview (questionnaire), obtaining specimens, analysis and storage of tissue, receiving pathology reports on resected lung tissue, and future follow up. Consent is obtained in the control subjects for interview, obtaining specimens; analysis and storage of samples, and future follow up. The right to refuse to participate in any and all aspects of the study is explicit in the interview and consent process and forms. The protocol, informed consent and contact letters have been amended to comply with NYS Civil Rights Law 79-1, which concerns genetic testing on human subjects.

The informed consent states that:

- a) Specimens will be retained for the purpose of biologic and genetic testing focused on the susceptibility to lung cancer or other lung diseases by virtue of inhaled toxins, how the body metabolizes them and their biologic effects. The specific tests to be conducted on collected specimens are for genes that include inhaled foreign compound processing genes, certain cancer-associated and inflammation associated genes and other genes, proteins and biological markers associated with the metabolism of foreign substances (Tests including phase I and phase II metabolizing genes, oncogenes,

tumor suppressor genes and other genes, proteins and biological markers associated with foreign compound metabolism, carcinogenesis, inflammation and other processes and their effects on lung disease). GWAS/genome-wide discovery-compatible consent is granted.

- b) Subject gives permission for testing these specimens to Dr Spivack and his research associates only.
- c) Confidentiality is assured through coding of information and specimens collected by the following procedures. The investigator will be blinded to subject's identity by having all meaningful identifiers (SSN, MRN, DOB) removed prior to any information and/or specimens being sent to Dr Spivack and his research associates at the AECOM Price Center for genetic testing and storage. Results of any tests performed will not be linked back to the person and information relating the identity of any subject will not be disclosed.
- d) Specimens will be stored, without subject identifiers, in a tissue repository with limited access.
- e) Organizations that may have access to the research records are representatives from the Food and Drug Administration, the National Institutes of Health, NYSDOH, AECOM IRB, MMC IRB and AECOM GCRC if applicable.
- f) The subject gives permission so that the results of testing on his/her specimens may be included in future publications and that all identifying information will be kept confidential.
- g) In addition to the above, a separate signature line will be included for permission to hold all specimens collected for an indefinite period of time for the tests listed in the consent and for collaborative studies specified below as addenda
- h) Permission for future contact of the subject by the research team is granted.

SPECIMEN RETENTION

A separate section of the informed consent will be included to obtain the subject's approval for the investigator to retain their specimens for an indefinite period of time. This, according to New York State (NYS) law, as interpreted by the NYS Department of Health, requires separate consent. The subjects will be asked to sign their name and check whether they agree or disagree to have their specimens stored indefinitely.

If this separate consent is not signed, the specimens will only be retained for the maximum length of time approved (currently 60 days) per NYS regulations.

CONFIDENTIALTY

Confidentiality is maintained by the following blinding procedure:

1. Initially, each subject's questionnaire and every specimen collected will be coded with a unique study number as well as the subject's initials, medical record number, the institution where specimens were obtained and date of collection. This unique study number will ultimately be the only number available to the investigator in order to correlate all the various specimens with the subject's questionnaire and pathology report.
2. All subject identifiers (with the exception of the subject's study number) will be removed by the study coordinators prior to being sent to the investigator for genetic analysis and storage. Additionally, all pathology reports will be sent to the investigator only after the subject's identifiers are removed and replaced by the appropriate study number. These measures ensure that any information disclosing the identity of the person from whom the

sample is taken has been removed prior to investigator receiving the sample for genetic analysis.

3. The results of any subject's genetic testing will be known only to Dr Spivack and his research associates and, through the blinding process outlined above, will not be able to be linked to any specific individual. No information relating to the identity of any subject will be disclosed.
4. Subjects will have the right to refuse to donate any or all of the additional specimens. Organizations that may have access to the research records are representatives from the Food and Drug Administration, the National Institutes of Health, New York State Department of Health, Montefiore Medical Center-IRB, AECOM-CCI.

Certificate of Confidentiality clause has been added in all forms as follows:

“As a way to protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health, which is funding this study. If information from this study was requested or subpoenaed by government agencies or the courts, we will use the Certificate to attempt to legally refuse to provide it. This is rare – in only a few cases did researchers have to use the Certificate, and it was honored most of the time, but not every time. There are several kinds of situations that the Certificate does not apply. For example, we are still required to report child abuse and some diseases, and we must make data available to the government for a review or evaluation of our research. The Certificate does not prevent you or a member of your family from voluntarily sharing information. Similarly, if an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information”.

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GROUP 4 SUBJECTS

(Original description, sans ^MCpG distribution/power Figures)

Specific Aims:

Aim 1. To determine group EBC DNA methylation patterns by high resolution tagged bisulfite genomic sequencing of three tumor suppressor genes (*DAPK*, *RASSF1A*, *PAX5B*), according to smoking status (current, former, never), and lifelong dose (pack-years) in a sample of HIV-infected smokers.

Aim 2. To pilot the comparison of EBC DNA methylation from HIV infected individuals to that from uninfected individuals, collected in other projects funded by other mechanisms.

Aim 3. To examine the stability of EBC DNA methylation patterns over time in HIV-infected smokers.

Hypothesis:

Smoking alters exhaled DNA methylation of known carcinogenesis genes in HIV-infected individuals in a dose-dependent manner; this methylation is higher than HIV-uninfected individuals, and stable over time.

Background:

Highly active antiretroviral therapy (HAART) has transformed HIV infection into a chronic disease. Today's HIV care clinics service a middle-aged population with real prospects for long-term survival. As mortality from traditional HIV-related infections and neoplasms

decreases, a new set of “intersecting epidemics” has now emerged - HIV infection, cigarette smoking, tobacco-related malignancies and cardiopulmonary disease.^{1,2} Cigarette smoking is epidemic among persons living with HIV/AIDS, with cohort-documented cigarette smoking prevalences at 50-60%, nearly three times the 20.9% prevalence of the general adult population.³⁻⁸ The NIH has highlighted the need to confront the smoking problem in persons living with HIV/AIDS (PLWHAs).⁹ Studies in the HAART era consistently demonstrate a risk of primary lung cancer approximately triple that of the general population.¹⁰⁻¹³

Clinical features of lung cancer in PLWHAs. Lung cancer is now second only to non-Hodgkin’s lymphoma as a cause of cancer-related mortality in PLWHAs.¹⁴ In contrast to lung cancer in the general population, in PLWHAs it occurs at a younger age, typically in males who are heavy smokers and present with symptomatic, advanced disease.¹⁵ In general, the degree of immunosuppression is not severe, with mean CD4+ lymphocyte counts at presentation exceeding 200 cells/uL.^{14,15} The aggressive course of lung cancers in PLWHAs has been noted repeatedly, with a dismal one-year survival of 10%.¹⁵⁻¹⁹

Biologic features of lung cancer in PLWHAs. Impaired immunologic surveillance has been proposed as a causative factor in some AIDS-related malignancies although there is no clear correlation of lung cancer incidence with CD4+ lymphocyte count.¹³ And while the oncogenic viruses HPV, HCV, EBV, HHV-8, and HIV itself are highly prevalent among PLWHAs²⁰ careful studies have failed to consistently identify genomic material of these oncogenic viruses in the respective lung tumors.¹⁵ Suggestions of enhanced genetic instability (microsatellite change) may contribute to the incidence of lung cancers in HIV infection, as may the mutagenic nucleoside reverse transcriptase inhibitors, perhaps as co-carcinogens.^{15,21}

Key hurdles to human studies in lung carcinogenesis: A means to procure lung cell derivatives from large numbers of individuals by simple noninvasive means, would permit direct human studies of lung carcinogenesis. For non-invasive sampling of the lung, spontaneously-exfoliated cells in sputum are a potential source of lung epithelium, and other cells. However, attempts to induce sputum are unsuccessful in >20-50% of asymptomatic individuals^{22,23}. Alternatively, exhaled breath is readily provided²⁴, and exhaled DNA may be isolated from its condensate²⁵⁻²⁷. Our lab has confirmed the presence of DNA²⁸ in >40 subjects. Methylation pattern analysis suggests that EBC-DNA is not simply a contaminant from the oropharynx (not shown); further validation is being pursued under an NCI-R21 grant (Spivack).

High resolution measurement of exhaled DNA methylation at specific loci: Several high resolution methods have been developed to determine the methylation status of cytosine at any given CpGsite, including bisulfite genomic DNA sequencing (BGS), and MS-based MassArray®. For this proposal, we will employ our recent tagged primer adaptation (tBGS) that avoids DNA cloning²⁸. The single base resolution detail and comprehensive maps exceed that available from conventional assays. Application to exhaled breath condensate specimens (EBC) represents a novel approach; our submitted data represent a first report. The data presented in Figure 1 attests to the promise of this technique in distinguishing DNA profiles according to smoking backgrounds, and as a potential tool for the early diagnosis of lung cancer. For example, in the initial 38 non-HIV infected subjects, we found higher aggregate DNA methylation in the three gene promoters to both smoking status ($p=0.0030-0.0045$), and to lung cancer case-status ($p=0.000-0.0060$, Fig.1). Pilot lung cancer case-control discrimination yields area under the curve (AUC) for receiver operator curves (ROC-AUC=0.84-0.91, $p=0.0070-0.0005$, not shown²⁹). Exhaled Micro RNA studies are pending.

Research Design and Plan:

Study Design. Specific Aims 1 and 2 will be studied in a cross-sectional manner, enrolling a convenience sample of PLWHA smokers attending the Montefiore Medical Center (MMC)

Infectious Diseases (ID) Clinic. Specific Aim 3 will employ a prospective design, collecting two specimens over time from a subset of the overall study sample.

Study Setting. Study related clinical activities will occur in the Montefiore ID Clinic. The MMC ID Clinic is the largest individual HIV care site in New York State, and it provides comprehensive medical care to over 2600 PLWHAs. A research suite, equipped with private examining rooms and space for storage of research records is located one floor below the clinic. The HIV-infected patient population has a mean age of 47 years. Forty-five percent are female, 54% Latino/a, 40% African American/Caribbean, 4% White, non-Latino/a. The patients report various overlapping transmission categories: 51% heterosexual, 19% IDU, 14% same sex contact, and 14% unknown. Approximately 68% of patients have CDC-defined AIDS, and 75% are on HAART. Two-thirds of patients report having smoked a cigarette within the past week (B. Zingman, MD, personal communication). PLWHA smokers in the clinic consume a mean of 14 cigarettes per day, and have been smoking for a mean of 29 years. Forty-eight percent report concurrent intranasal or inhaled cocaine use, and 47% report concurrent marijuana use. The ID Clinic owns and maintains a modern exhaled carbon monoxide (eCO) monitor for biochemical confirmation of smoking status in ongoing smoking-related research projects.

Laboratory Resources. *Spivack lab:* A fully equipped laboratory (1,000 sq. ft.) set up for modern biochemistry, molecular genetics and cell biology within the Center for Genetic & Translational Medicine (CGTM), at the newly-constructed Price Center on the AECOM main campus. All equipment typical of a modern molecular biology and genetics laboratory. *Adjacent laboratory resources:* DNA sequencing core, equipped with multiple conventional dideoxy-capable capillary set-up (ABI 3130 or equivalent); the informatics and statistical resources of the AECOM Epigenomics Center (MFazzari) and BISR (TWang).

Subject Accrual. We plan to enroll 100 HIV-infected subjects over a period of six months. The research assistant will attend two clinic sessions weekly during this time, and will aim to recruit two new subjects of the 50 patient subjects seen at each clinic session. Numerous prior low-risk studies have successfully employed these strategies to meet comparable or larger accrual targets in the ID Clinic. For Specific Aim 3, the research assistant will maintain a log of enrolled subjects and identify those scheduled for clinic visits at least three months after enrollment. Virtually all clinic patients are scheduled for follow-up at least every three months. Subjects from the original cohort attending a follow-up visit at three or more months post-enrollment will be invited to complete a second study visit, until the follow-up cohort of 30 subjects is assembled, to address the issue of exhaled DNA methylation stability over time.

Study Visit Activities:

- a) *Clinical Questionnaire:* At point-of enrollment, participants will complete a previously validated questionnaire containing questions pertaining to socio-demographic characteristics, tobacco and other substance use, history of lung disease, as well as an additional module pertaining to HIV infection, opportunistic illnesses, and antiretroviral exposure. Participants will also undergo exhaled carbon monoxide testing using the BedfontpiCOSmokerlyzer at baseline in order to confirm smoking status.
- b) *Exhaled breath condensate collection (EBC):* Briefly, a disposable inner R-tube® (Respiratory Research, Charlottesville, VA) of polypropylene with one way valve, comes in contact with patients breath. There is additionally a reusable outer freezer-cooled cooling sleeve (-80°C) and insulating layer, The subject quietly breaths (at normal tidal volume with a sigh each minute) into the disposable inner tube by mouth, with nose clips for 15 minutes, while reading or engaging in another quiet activity. At the end of the session, the condensate specimen is sealed, and transported to the Spivack laboratory for DNA analysis.

- c) Saliva collection: Saliva may be collected twice. This will be accomplished by having subjects: (a) spit into special collection device and/or (b) chew on a cotton wool swab for 30 to 60 seconds.

Methylation data handling: The presence, partial presence, or absence of methylation at a CpG site is assessed by comparing bisulfite treated to untreated genomic DNA sequence by tBGS, using software sequence alignment, and verified at CpG sites by direct review of cycle sequence chromatogram tracings. The data spacially compresses to a single metric, percent of sites methylated (methylation “density”). Alternatively, another approach is to preserve spatial patterns across different CpG sites in a given gene promoter; regression of mean methylation rates in a given region can serve as group summary (Fig. 1).

Statistical analyses: We will employ multivariate modeling of individual *a priori* hypotheses to be tested. Principle analysis of the *main effects of smoking* (Aim 2) on EBC methylation density and spatial patterns, will be based on a linear regression with potential covariates (such as age, HIV infection, and underlying lung disease) included in the model. Principle analysis of the *main effects of HIV infection* (Aim 3) will consider potential covariates (age, underlying lung disease, smoking status). The comparison group will be that from an age- and smoking status frequency-matched cohort, from other Spivack laboratory projects. The EBC from these non-HIV infected individuals is being analyzed for the same markers by the same techniques, and is the source of pilot data (Fig. 1,2). For *measurement of methylation map stability* (Aim 3), we will use a repeated measures design. Corrections for multiple comparisons and measurements will be performed. False discovery approaches will be used. The Biostatistics Resource will be enlisted.

Power: This is a pilot discovery study. We will prioritize smoking and HIV infection as the primary, prioritized endpoints of interest. While we have no pilot EBC-DNA methylation variance data on those with HIV infection (n=110) versus those without HIV infection (n=75), if we assume similarities to data we have piloted in the non-HIV population we will have sufficient power for the analyses described.

Timeline: We completed accrual within the first six months (from January to July, 2009), The Spivack lab will analyze the EBC from the recruited ~100 HIV-infected individuals. The 75 non-HIV-infected individuals’ data (from a separate, NCI-funded project) will be available by that same time point. The team will then analyze the data using multivariate linear and regression analyses, for reporting purposes. A manuscript, and an NIH R01 application, will result.

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GROUP 5 SUBJECTS

(Collecting extra bronchial brushes in a subset of Bronchoscopy cases)

Introduction: Using the same bronchial brush protocol as previously, we expect to get extra brushes for each tissue phenotype in a subset of 50 lung cancer (case) individuals undergoing bronchoscopy for clinical indications (e.g. diagnosis, airway therapeutics/palliation) . Three tissue phenotypes are of interest, and defined by the combination of white light (WB) and LIFE (fluorescent) bronchoscopy: (a) obvious visible endobronchial tumor tissue; (b) visible dysplastic tissue (by reflectance); and (c) visibly normal bronchial tissue (by reflectance). Laser induced fluorescent endoscopy has been FDA approved for detection of dysplasia for >5 years in the endobronchial epithelia, is innocuous, and prolongs under standard WB clinical procedures ~10-15 minutes. The procedure is performed through similar bronchoscope as standard white light bronchoscopy, except the light source is altered. The instrument is in clinical use in the MMC bronchoscopy suite (Dr. C Shah and Dr. A Sadoughi)).

The intent for this subset of patients is to get 3-5 brushes per tissue phenotype per subject. Thus, 9-15 brushes per case subject will be the intent. The protocol will be in use for appropriate bronchoscopy cases of Dr. C Shah and Dr. A Sadoughi, the interventional pulmonologist, as she has longstanding skills in LIFE examination, as well as advanced airway procedures (stents, lasers, cryotherapy, photocoagulation, etc.) and patency maintenance.

After the WB procedure for clinical purposes is completed, checking that the patient is tolerating that procedure well, we will exchange scopes to the LIFE bronchoscope. The LIFE bronchoscope will be advanced to an: (a) area of overt (WB+LIFE-confirmed) malignancy, and cytologically brush (abrade) the bronchial surface of that area with three to five separate brushes, each intended for a different set of assays (DNA, RNA, microRNA, metabolites, cytopathology) each requiring different buffers. The procedure will go to five brushes per area as long as patient and mucosa are tolerant. We will repeat the procedure, collecting three to five brushes for each airway tissue phenotype: (b) dysplasia represented by brown discoloration on LIFE bronchoscopy; and (c) normal endobronchium by WB and LIFE bronchoscopy consensus.

Procedure will be immediately stopped for significant bleeding, refractory cough, or any clinically apparent subject intolerance (hypoxia, sedation inadequacy/refractoriness, etc.) to the extra brush collection.

Incremental risk for 15 total brushes, versus current four collected, is for bleeding, cough, and prolongation of procedure under mild-moderate sedation, estimated as <0.1%, according to literature, in turn based on (i) risk of more advanced procedures (transbronchial biopsies, etc), and (ii) our extensive clinical and recent research experience.

**ALBERT EINSTEIN COLLEGE OF MEDICINE
MONTEFIORE MEDICAL CENTER**

Individual Information and Consent Form, Group 1 Surgery

You are being asked to join this research study.

The title of the study is: Genetics of Lung Disease (Exhaled Breath Markers in Lung Carcinogenesis)

The study is being done under the supervision of:

Principal Investigator (Researcher Study Doctor): Simon Spivack MD

Office Address: 1301 Morris Park Avenue

Price Center Room 268 Bronx, NY 10467

Telephone #: 718 678-1040

Protocol #: 2007-407-000

Funded by: National Institute of Health and Department of Defense.

DO I HAVE TO TAKE PART IN THIS RESEARCH STUDY?

Your participation is voluntary. This means that you decide whether or not you want to join the study after speaking with the researcher, or other member of the research team.

If you decide to take part you will be asked to sign this consent form. Your signature means that you agree to be a subject in this research.

After reading this form and having a discussion about what it says, you should ask all the questions you want to ask. You should take as much time as you need to make a decision.

If you do not understand some of the terms used in this form, ask the person who is discussing the study with you to give any additional information that may make this easier to understand.

You do not have to consent to participate in the study immediately, or ever. Take time to decide whether or not you wish to join. You may take home a copy of this consent form to think about it or discuss the information with family or friends before you decide.

If you decide not to participate, the care providers at this facility will give you all of the standard care that is appropriate for you.

You will be given a copy of this form whether or not you agree to participate in this study. Do not sign the form unless you have had all your questions answered and understand exactly what is involved.

If you decide to take part you are still free to withdraw at any time without giving a reason. This will not affect your care and you will continue to be treated at this facility.

The form discusses:

WHAT THE RESEARCHERS WILL LEARN FROM THE RESEARCH

WHAT WILL HAPPEN TO YOU DURING THE RESEARCH
WHAT RISKS AND/OR DISCOMFORTS YOU MIGHT EXPECT/EXPERIENCE AS A RESEARCH SUBJECT
IF YOU CAN EXPECT ANY BENEFITS, AND ARE THERE ANY ALTERNATIVES TO THIS RESEARCH FOR YOUR CONDITION.
WHY HAVE I BEEN ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being asked to take part in a research study because you will soon be having a surgical removal of your lung for clinical indication.

WHY IS THIS RESEARCH STUDY BEING DONE?

- This research will attempt to establish a relationship between the molecular changes that occur in cells from the mouth, saliva, sputum, exhaled breath and blood as they relate to the development of lung disease. If this relationship can be proven, it may be possible in the future to test for certain lung diseases with a simpler, non-invasive laboratory test.
- Dr. Simon Spivack, the principal investigator, is conducting a research investigation to determine whether the activity of certain genes and proteins in the lung and other tissues increases with exposure to cigarette smoke or environmental hazards. This increased activity might impact the development of lung disease. Genes instruct proteins to control and direct many activities of cells in the human body. The genes of interest to this investigation include inhaled foreign compound-processing genes, certain cancer-associated genes, and other genes, proteins and biological markers associated with the metabolism of foreign substances, cellular processes, or other lung disease-related processes. The activity of genes and proteins found in the lung are thought to parallel that detected in blood, saliva, sputum, exhaled breath condensate (moisture) and mouth cells. This is unproven. Additionally, the relationship of these genes' activity to lung diseases, including lung cancer, remains unproven.

Also the causes of discordance between the rare development of upper airway/laryngeal cancers versus the ten-fold more common development of lung cancers in smokers remains unclear. By this study we wish to perform an intra-individual molecular comparison of the two anatomic airway sites. Such host resistance factors in the upper airway might serve to enlighten the path to lower airway/ lung cancer prevention

HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

- You will be one of approximately 2000 who will be participating in this study at Montefiore Medical Center and Albert Einstein College of Medicine.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

If you agree, we will tell you more about the study and answer any questions you may have by telephone, at your anesthesia screening appointment in the hospital before your surgical procedure.

We expect that you will be in this research study from the time informed consent is signed until you complete your surgery.

The interview process and specimen collection takes approximately 40 minutes.

PROCEDURES:

- DURING SURGERY:** Two (2) lung tissue specimens will be obtained from lung tissue removed as part of your surgeon's treatment or diagnosis of your lung problem. The extent, approach or amount of tissue removed is unchanged as a result of participation in this study. No tissue will be removed solely for this study. The researchers will process tissue samples which are not otherwise needed for diagnosis of your condition. The lung tissue will then be compared to the blood and other cells you may have donated. Your surgery and post-operative recovery are not affected as a result of your participation in this study.
- If you agree to participate, this surgical tissue will be forwarded from the Surgeon and Department of Pathology at Montefiore Medical Center to Dr. Spivack and his research associates at the Price Center, Albert Einstein College of Medicine, Bronx, NY.
- In addition, this consent gives permission to the investigator to obtain a copy of the pathology report for your lung tissue that is sent by your physician to pathology for diagnosis. These reports will not be sent with any information regarding your personal identity.
- You will be asked to complete a questionnaire regarding the amount you have smoked, your diet, other environmental exposures, medication and family history. This information is crucial to this study. The questionnaire will be administered by research nurse study staff and takes about 15 minutes to complete.
- There are six (6) specimens study staff would like to collect:
 - Extra tubes of blood (30 mls or about 2 tablespoons of blood) will be drawn at the same time as your clinically indicated pre-anesthesia blood tests or at the same time your IV is inserted prior to your bronchoscopy, to avoid extra needle sticks.
 - A collection of mouth cells by rinsing your mouth with an over-the-counter mouthwash solution.
 - A manual spinning soft brush will be held against the lining of each cheeks four times to collect additional mouth cells.
 - A collection of your exhaled breath condensate (EBC). This will be done by having you rinse your mouth with water and then breathing normally into a disposable portable mouthpiece for 10-15 minutes to collect 1 ml (less than one quarter teaspoon) of EBC. It may be necessary to wear a nose clip during the collection.
 - A collection of your saliva, by spitting into a cup. A second collection of your saliva, obtained by chewing on a cotton-wool swab called a salivette for about 30 to 60 seconds, will be obtained. One can measure cotinine, reflective on smoking, in the saliva, in addition to other measurements.
 - A collection of your sputum (phlegm from your throat) will be collected by taking a deep breath and coughing sputum directly into a collection cup. If you are unable to collect sputum this way we may give you a saline nebulizer for 10 minutes to moisten the airway and then ask you to take a deep breath and cough sputum directly into a collection cup.The six specimens are collected by research staff or phlebotomy staff. Specimen collection takes about 20-30 minutes.

In addition, this consent gives permission to the investigator to obtain a copy of the pathology report for your lung tissue that is sent by your physician to pathology for diagnosis. These reports will not be sent with any information regarding your personal identity.

ADDITIONAL TESTS ON YOUR SAMPLE: In the future because of the acquisition of new knowledge through research and advances in techniques in the field of genetic testing, the investigator may conduct other biologic and genetic testing focused solely on the susceptibility to lung cancer and other lung diseases caused by inhaled toxins, or other substances. This gives consent for possible further testing on your specimens. The additional tests would be focused on foreign compound-processing genes, cancer-associated genes and other genes, proteins and biologic markers associated with the metabolism of foreign substances, cellular function, and other lung disease-relevant phenomena. All previously mentioned assurances for your confidentiality will be maintained. The results of all genetic testing will not be made available to you. If you would like to speak with a genetics counselor about general information concerning the storage of genetic specimens, you may call one.

Since the significance of these tests are not known for you or anyone else at this point, we will not disclose the results of the molecular or genetic testing. No formal counseling will be provided under the research study. If you request, you will be referred to a genetic counselor. You or your insurance carrier will be responsible for the genetic counselor's fee.

WILL THIS STUDY INVOLVE GENETIC RESEARCH and/or TESTING

This research study is designed to explore the genes and molecules that may be responsible for the susceptibility and/or development of lung disease in anticipation of establishing molecular screening strategies for the early detection of lung diseases, including cancer.

- Tests conducted under this research study may reveal genetic information.
- GENETIC COUNSELING INFORMATION:** You may wish to obtain professional genetic counseling prior to signing the informed consent. A genetic counselor is a person qualified to provide information about what the results of this type of test may mean to you and your family. You or your insurance company will be responsible for the cost of these services.

WHAT ARE THE POSSIBLE SIDE EFFECTS, DISCOMFORTS, RISKS OR INCONVENIENCES I CAN EXPECT FROM BEING IN THIS RESEARCH STUDY?

Here is a list of the known risks associated with this research:

- Questionnaire:** Occasionally, the discussion about smoking history or environmental contaminant exposure during the interview process may provoke anxiety.
- Blood:** Rarely, is an extra needle stick required to collect the blood specimens. The risks involved in blood sampling are infection (rare) and bruising and pain (occasionally).
- Mouth:** swabs with soft brushes rarely may cause discomfort and bleeding. The mouthwash solution causes a tingling sensation that resolves quickly and rarely is a cause for discomfort.
- Exhaled breath condensate:** collection is a non-invasive test and does not have any known risk. You may feel uncomfortable from breathing into a tube and possibly wearing a nose clip for 10-15 minutes.
- Saliva:** collection does not have any known risk.

- Sputum: The risk regarding the sputum induction include cough, fall in oxygen level in the blood, and bronchospasm especially in asthmatics.

WILL THE RESULTS OF THIS STUDY OR ANY OF THE PROCEDURES AFFECT MY INSURABILITY?

The tests done under this study will not affect your ability to get or keep medical, health or life insurance.

ARE THERE LIKELY TO BE ANY BENEFITS TO TAKING PART IN THIS RESEARCH STUDY?

You will not benefit from being in this research study. However, there may be a general benefit to society by the furthering of scientific knowledge. The information gained by using your tissues will help us better understand lung disease and help us establish molecular screening strategies for the early detection of lung disease and lung cancer.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS RESEARCH STUDY?

- You may choose not to participate in this study.

WILL I BE PAID FOR BEING IN THE STUDY?

- If you agree to take part in this research study, we will compensate you for your time and expenses (\$5.00 each for 6 lab tests as outlined in procedure section for a maximum amount of \$30.00).

If you do not complete the study, your payment will be prorated. We will be collecting your social security number in order to process your payment.

WHO MAY SEE MY RECORDS?

- The research records will be kept private and your name will not be used in any written or verbal reports.
- Your research records and medical records may be inspected by members of the research team and other institutions that participate in this study. These are: The U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), Department of Defense (DoD) research monitors, Department of Health and Human Services (DHHS) offices, New York State Department of Health (NYSDOH), Governmental agencies in other countries, Federal agencies involved with research, governmental agencies to whom certain diseases (reportable diseases) must be reported.
- The researcher and research staff will review your medical records and will keep the information private.
- The research records will be kept in a secured manner and computer records will be password protected.

- The people who reviewed this research study as members of the Albert Einstein College of Medicine Committee on Clinical Investigations (CCI) and the Montefiore Medical Center Institutional Review Board (IRB) may also review your research and medical records.
- The Office of Human Research Protections (OHRP) may also review your research study records.
- The research records will be kept in a secured manner and computer records will be password protected in the Albert Einstein College of Medicine Clinical Research Center (CRC).
- The Clinical Research Center staff, as well as the research personnel authorized by the researcher will have access to these records.
- All of these groups have been requested to keep your name private.

Certificate of Confidentiality

As a way to protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health, which is funding this study. If information from this study was requested or subpoenaed by government agencies or the courts, we will use the Certificate to attempt to legally refuse to provide it. This is rare – in only a few cases did researchers have to use the Certificate, and it was honored most of the time, but not every time. There are several kinds of situations that the Certificate does not apply. For example, we are still required to report child abuse and some diseases, and we must make data available to the government for a review or evaluation of our research. The Certificate does not prevent you or a member of your family from voluntarily sharing information. Similarly, if an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

If there is a physical injury as a result of this research, only immediate, essential, short-term medical treatment as determined by the participating hospital, will be available for the injury without charge to you personally.

- No monetary compensation will be offered.
- You are not waiving any of your legal rights by signing this informed consent document. If additional treatment is required as a result of a physical injury related to the research, necessary medical treatment will be provided to you and billed to your insurance company or to you as part of your medical expenses.
- Immediately report any discomforts, problems or injuries you experience during the course of your participation in the study to Dr. Simon Spivack at 718 678-1040 between the hours of 9am to 5pm.

WILL THERE BE ANY COSTS TO ME?

- There will be no costs to you for participating in this study.

Can I be asked to stop participating in this study before the study is finished?

- If the study goal has been reached, you can be asked to stop participating.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

Researcher's Name: *Dr. Simon Spivack*

Office Address: 1301 Morris Park Avenue Price Center 268 Bronx, NY 10467

Office Phone: 718-678-1040

- If any questions arise related to this research project, or you believe you have any injury related to this study, you can call the researcher above.
- If you have questions regarding your rights as a research subject, you may also call the Manager of The Albert Einstein College of Medicine Committee on Clinical Investigations at (718) 430-2253, Monday through Friday between 9 AM and 5 PM.

WILL ANY OF THE SAMPLES (BLOOD, TISSUE, DNA) TAKEN FROM ME BE USED FOR FUTURE RESEARCH STUDIES?

WILL ANY OF THE SAMPLES (BLOOD, TISSUE, DNA) TAKEN FROM ME BE USED FOR FUTURE RESEARCH STUDIES?

FUTURE RESEARCH ON **DE-IDENTIFIED SPECIMENS** Introduction:

In addition to the current research you are consenting to under this research study, Dr. Simon Spivack or other researchers at this or other institutions, and federal agencies such as NIH, may wish to study the samples in future research, including genetic analysis. These samples, taken from your body, during this medically necessary surgery your doctor has recommended would **NOT** be linked back to you. No one will know your name, initials, DOB, MRN, SS# or other identifiers or protected health information. Therefore, no additional risks to privacy are expected from this sharing. All names and other identifiers are under double lock and password, and held by the research coordinator only, not the scientists. Your specimens and data may be used for future research, even though the purpose of the future research is not known at this time. At this time, the researcher does not know what the future studies will be. Your specimens and data may also be submitted to a tissue/cell/DNA bank. The specimens may be kept for a long time and may exceed 50 years.

In some research using human blood or tissue, the specimens and data their parts may enable researchers to develop medical tests or treatments that have commercial value. You will not receive any money that may result from any such commercial tests or treatments.

SPECIFIC FUTURE RESEARCH TESTING ON YOUR SURGICAL LUNG TISSUE:

As a part of examining the molecular changes that lead to lung cancer development and response to treatment, the extra tissue from your lung biopsy specimen (if there is evidence of tumor in it) will, with your specific permission in a separate line below, be implanted in laboratory mice to study their genetic characteristics and to test various chemotherapeutics and anticancer agents. If you agree to participate, this surgical tissue will be forwarded from the Surgeon and Department of Pathology at Montefiore Medical Center to the laboratories of Drs. Edward Schwartz and Roman Perez-Soler and their research associates. You will remain anonymous, these collaborators will not be able to identify you.

In order to allow the greatest amount of research to be performed on the tissue you donate and learn the greatest amount possible, researchers for this study may share your tissue, blood, and DNA with other scientists and researchers at other universities, government agencies and labs, hospitals, health-related companies, or research institutes. Additionally, some samples may be

taken to explore stem cells of origin in the laboratory of Dr. Yakov Peter and colleagues, again with your specific permission in a separate line below. You will remain anonymous, these collaborators will not be able to identify you.

Your participation in this part of the research is optional. The extent of surgical procedure or amount of tissue removed will not be affected as a result of participation in this part of the study. The researchers will use the tissue samples which are otherwise not needed for the diagnosis of your condition.

The purpose of this part of the study is to examine different molecular changes that occur in lung cancer and to correlate them with response to different anti-cancer treatments. As a part of the study, the research coordinators [without access (i.e., “blinded”) to your genetic test results will review your medical record to obtain the stage, type of tumor, your age, ethnicity, the type of treatments that you received for your cancer and the outcome including survival, if available. This information will help the researchers to help understand what they find or test have any correlation with the actual outcome from your cancer.

All of this clinical information collected by the research coordinators will be stored with a study number. No one will know your name or protected health information. Therefore, no additional risks to privacy are expected from this data collection. A similar review may be done also in the future either from your medical record or cancer registry to record the outcome or survival from your cancer. These data help the researchers to study whether a medical test that they are studying predicts the good or bad outcome from the cancer.

Your de-identified health-related information from your medical record will be made available to the investigators for review, and may be shared with other scientists and researchers at other universities, government agencies and labs, hospitals, health-related companies, or research institutes.

*The scientists doing the research testing will not know who you are. The scientific information will be stored with a generic study number assigned to you that is **not** visibly linked to your initials, DOB, MRN, SS# or other identifiers. The scientists will only use/be aware of this number, not your initials, DOB, MRN, SS# or other identifiers. The research coordinator will know your initials, DOB, SS# or other identifiers, but will not know the results of your research laboratory/genetic tests. Therefore, no one person will have the link of your initials, DOB, MRN, SS# or other identifiers and the research laboratory/genetic tests. No researcher will know your name or protected health information. This “uncoupling” of information allows you to remain anonymous to the researcher.*

PROCEDURE: There is no additional surgical lung procedure for this part of the study. The extra tissue from your biopsy specimen, not needed for your diagnosis or care or other research purposes, may be implanted in mice for further molecular testing and various cancer treatments.

RISK: There is no additional risk in participation in this part of the study. (a) The tissue to be tested will already be removed from you solely to treat your cancer. (b) The potential for loss of privacy is a very remote risk, because: (i) uncoupling the identifier information from the research laboratory/genetic information prevents this information from being assembled; (ii) identifier information is double password protected and locked by the research coordinators; (iii) The scientific researchers involved have done this on over 1000 patients in this protocol without a loss of privacy; and (iv) this is a standard, widely-accepted approach used nationally, on tens of thousands of subjects.

BENEFITS: You will not benefit from participating in this part of the research study. However, the information learned from this research may, in the future, benefit other people with the same disease. The results from these tests are for research purposes only, and will **not** be available to you or your treating physician.

PARTICIPANT:

PLEASE INDICATE YOUR CHOICE BY INITIALING ONE (1) or MORE OF THE FOLLOWING OPTIONS

I consent to have my specimens used for all future research studies.

I consent to have my specimens used for future research studies only for the study of

_____.

I consent to have my specimen implanted in laboratory mice and stored and shared with collaborators in future studies.

I consent to have my specimen pursued for lung stem cells, in future studies.

I do **NOT** consent to have my specimen implanted in laboratory mice for future studies.

I do **NOT** consent to have my specimen pursued for lung stem cells in future studies.

I do **NOT** consent to have my specimens used for any future research studies. (The specimens will be destroyed at the end of the current study.)

WHAT IF NEW INFORMATION BECOMES AVAILABLE?

If the research study doctor obtains new information that might lead you to change your mind about continuing in this study, the research study doctor will tell you about it.

If you decide to withdraw, the research study doctor and your personal doctor will make arrangements for your care to continue.

MAY I STOP THE STUDY AT ANY TIME?

Your participation in this study is voluntary, and you may withdraw from the study at any time without giving a reason.

If you agree to participate and withdraw at a later time, some of your information may have already been entered into the study and that will not be removed.

In addition, you may be asked to return to the research study doctor again for any final tests in order to close the record and tests or monitoring that are necessary for your health as a result of your participation. These results may be recorded.

Your treatment by doctors and staff at the institution(s) involved in this study, now and in the future, will not be affected in any way if you agree to participate and withdraw later.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS RESEARCH STUDY?

Your participation in this study is voluntary.

You do not waive any of your legal rights by participating in this research study.

Your treatment by doctors and staff at the institution(s) involved in this study, now and in the future, will not be affected in any way if you refuse to participate or if you enter the study and withdraw later.

Informed Consent Signature Page

The following is a list of items we discussed about this research study. If you have any questions about any of these items, please ask the person who is discussing the study with you for more information before agreeing to participate.

- What the study is about.
- What I must do when I am in the study.
- The possible risks and benefits to me.
- Who to contact if I have questions or if there is a research related injury.
- Any costs and payments.
- I can discontinue participating in the study at any time without penalty.
- Other choices.
- All written and published information will be reported as group data with no reference to my name.
- I have been given the name of the researcher and others to contact.
- I have the right to ask any questions.

_____	_____	_____
Printed Name of Participant	Signature of Participant	Date

_____	_____	_____
Printed Name of Person conducting the Informed Consent Process	Signature of Person conducting the Informed Consent Process	Date

**ALBERT EINSTEIN COLLEGE OF MEDICINE OF YESHIVA UNIVERSITY
MONTEFIORE MEDICAL CENTER**

Información para el participante y formulario de consentimiento

Grupo 1, Cirugía

Se le está pidiendo que participe en este estudio de investigación.

El nombre del estudio es: Genética de la enfermedad pulmonar (marcadores en aire exhalado en la carcinogénesis pulmonar)

El estudio se está llevando a cabo bajo la supervisión de:

Investigador principal (doctor del estudio de investigación): Simon Spivack, MD

Dirección de oficina: 1301 Morris Park Avenue,
Price Center Room 268 Bronx, NY 10467

Número de teléfono: 718-678-1040

Número de protocolo: 2007-407-000

Declaración: El investigador principal, Dr. Simon Spivack, ha recibido una patente de una forma específica de analizar la metilación (cambios) del ADN que se llama GC (guanina y citosina) etiquetada con la secuenciación genómica de bisulfito. Este método se está usando en el estudio actual. En base a los datos de ésta y otras investigaciones, puede ser que el posible valor económico de este método de prueba aumente. De esta manera, la institución y el investigador principal tienen un posible interés económico en el resultado de este estudio.

¿TENGO QUE PARTICIPAR EN ESTE ESTUDIO DE INVESTIGACIÓN?

- Su participación es voluntaria. Esto quiere decir que usted decide si quiere participar el estudio o no después de hablar con el investigador, u otro miembro del equipo de investigación.
- Si decide participar en el estudio, le pediremos que firme este formulario de consentimiento. Su firma significa que usted acepta ser participante en esta investigación.
- Después de que usted lea este formulario y haya hablado sobre lo que trata el formulario, usted debe preguntar todo lo que quiere saber. Debe tomarse el tiempo que necesite antes de tomar una decisión.
- Si no entiende algunas de las palabras que se usan en este formulario, pídale a la persona con la que usted está hablando sobre el estudio que le dé información adicional que le permita entender más fácilmente.
- Usted no tiene que aceptar participar en el estudio ahora o en el futuro. Tómese su tiempo para decidir si desea participar o no. Usted puede llevarse una copia de este formulario de consentimiento para que lo piense o pueda comentar la información a su familia o sus amistades antes de tomar una decisión.

- Si usted decide no participar, los proveedores de atención médica en este centro le brindarán toda la atención médica habitual apropiada para usted.
- A usted se le dará una copia de este formulario, ya sea si acepta participar o no en este estudio. No firme el formulario a menos que le hayamos respondido a todas sus preguntas y entienda exactamente de lo que trata el estudio.
- Si decide participar en el estudio, todavía tiene la libertad de retirarse del estudio en cualquier momento sin tener que dar ninguna explicación. El retirarse del estudio no afectará su atención médica y usted continuará su tratamiento en este centro.
- El formulario trata sobre:

LO QUE LOS INVESTIGADORES SABRÁN DE LA INVESTIGACIÓN. LO QUE LE PASARÁ A USTED DURANTE LA INVESTIGACIÓN.

LOS RIESGOS Y/O LAS MOLESTIAS QUE PUEDE ESPERAR/PRESENTAR COMO PARTICIPANTE DE LA INVESTIGACIÓN.

SI USTED PUEDE RECIBIR ALGÚN BENEFICIO, Y SI ¿HAY ALGUNA ALTERNATIVA A ESTA INVESTIGACIÓN PARA SU ENFERMEDAD?

¿POR QUÉ ME HAN PEDIDO QUE PARTICIPE EN ESTE ESTUDIO DE INVESTIGACIÓN?

Le estamos pidiendo que participe en el estudio de investigación porque pronto usted tendrá una extracción quirúrgica del pulmón por indicación clínica.

¿POR QUÉ SE ESTÁ HACIENDO ESTE ESTUDIO DE INVESTIGACIÓN?

- Esta investigación tratará de establecer la relación entre los cambios moleculares que ocurren en las células de la boca, la saliva, el esputo, el aire exhalado y la sangre en relación al desarrollo de la enfermedad pulmonar. Si esta relación se puede probar, puede ser posible que en el futuro se hagan pruebas para detectar ciertas enfermedades pulmonares con una prueba de laboratorio más simple.
- El Dr. Simon Spivack, el investigador principal, es el que está llevando a cabo la investigación para determinar si la actividad de ciertos genes y proteínas en el pulmón y en otros tejidos aumenta con la exposición al humo del cigarrillo o a los peligros ambientales. El incremento de esta actividad puede tener un efecto en el desarrollo de la enfermedad pulmonar. Los genes ordenan a las proteínas a controlar y dirigir muchas actividades de las células en el cuerpo humano. Los genes que son de interés para esta investigación incluyen los genes de procesamiento de compuestos extraños inhalados, ciertos genes relacionados con el cáncer y otros genes, marcadores proteínicos y biológicos relacionados con el metabolismo de sustancias extrañas, procesos celulares u otros procesos relacionados con la enfermedad pulmonar. Se cree que la actividad de los genes y las proteínas encontradas en los pulmones son iguales a aquella detectada en la sangre, la saliva, el esputo, el condensado de aire exhalado (humedad) y las células de la boca. Esto no está probado. Además, la relación de la actividad de estos genes con las enfermedades pulmonares, incluyendo el cáncer de pulmón, continúa sin probarse.

¿CUÁNTAS PERSONAS PARTICIPARÁN EN ESTE ESTUDIO DE INVESTIGACIÓN?

- Usted será una(o) de aproximadamente 2 000 personas que estarán participando en este estudio en el Centro Médico Montefiore (*Montefiore Medical Center*) y en la Escuela de Medicina Albert Einstein (*Albert Einstein College of Medicine*).

¿QUÉ SUCEDERÁ SI PARTICIPO EN ESTE ESTUDIO DE INVESTIGACIÓN?

Si usted decide participar, le diremos más sobre el estudio y responderemos cualquier pregunta que tenga por teléfono, en su cita para las pruebas de anestesia en el hospital antes de su procedimiento quirúrgico.

Esperamos que usted participe en este estudio de investigación desde el momento que usted firme el consentimiento informado hasta que complete su cirugía.

El proceso de la entrevista y la recolección de muestras toman unos 40 minutos.

PROCEDIMIENTOS:

- **DURANTE LA CIRUGÍA:** Se obtendrán dos (2) muestras del tejido pulmonar del tejido pulmonar extraído como parte del tratamiento o diagnóstico del cirujano para su problema pulmonar. El alcance, enfoque o cantidad de tejido extraído no cambia como resultado de su participación en este estudio. No se extraerá nada de tejido para uso exclusivo de este estudio. Los investigadores procesarán las muestras de tejido las cuales, en otras circunstancias, no se necesitan para hacer diagnósticos para su enfermedad. Luego, el tejido pulmonar se comparará con la sangre y otras células que usted haya donado. Su cirugía y recuperación después de la operación no cambian como resultado de su participación en este estudio.
- Si acepta participar, este tejido quirúrgico se enviará del cirujano y del Departamento de Patología del Centro Médico Montefiore al Dr. Spivack y a sus asociados de investigación en el Centro Price (*Price Center*, por su nombre en inglés), en la Escuela de Medicina Albert Einstein, Bronx, NY.
- Además, este consentimiento da su permiso al investigador para que obtenga una copia del informe patológico de su tejido pulmonar que envía su médico a patología para el diagnóstico. Estos informes no se enviarán con ninguna información sobre su identidad personal.
- Le pediremos que complete un cuestionario sobre la cantidad de cigarrillos que ha fumado, los alimentos que come, otras exposiciones ambientales, medicamentos, y antecedentes familiares. Esta información es de suma importancia para este estudio. Un(a) enfermero(a) de investigación del personal del estudio le tomará el cuestionario y durará cerca de 15 minutos completarlo.
- El personal del estudio recolectará seis (6) muestras:
 - Se le extraerán tubitos adicionales de sangre (30 mililitros o unas 2 cucharadas de sangre) al mismo tiempo que se le hagan las pruebas de sangre preanestésicas por indicación clínica o al mismo tiempo que se le introduzca la vía intravenosa antes de la broncoscopia, para evitar pinchazos de agujas adicionales.

- Se recolectarán células de la boca enjuagándose la boca con una solución de enjuague bucal que es sin receta médica.
- Se recolectarán células de la boca adicionales sosteniendo cuatro veces un cepillo suave de uso manual contra el revestimiento de cada mejilla.
- Se recolectará una muestra de condensado de aire exhalado (CAE). Esta muestra se le tomará por medio del enjuague de la boca con agua y luego respirará normalmente en una boquilla portátil descartable de 10 a 15 minutos para recolectar 1 mililitro (menos de un cuarto de cucharadita) de condensado de aire exhalado. Pueda que sea necesario usar una pinza nasal durante la recolección de la muestra.
- Se recolectará una muestra de su saliva, tendrá que escupir en un vasito. Se recolectará una segunda muestra de su saliva la cual se obtendrá masticando un hisopo de algodón que se llama salivette de 30 a 60 segundos. Uno puede medir la cotinina, que se refleja al fumar, en la saliva, aparte de otras medidas.
- Se recolectará una muestra de esputo (flema de la garganta). Respirará profundamente y toserá el esputo directamente en el vaso para la muestra. Si usted no puede recolectar el esputo de esta manera, podemos darle un nebulizador salino por 10 minutos para humedecer las vías respiratorias y luego le pediremos que respire profundamente y tosa el esputo directamente en el vaso para la muestra.

El personal de la investigación o el personal de flebotomía recolectarán las seis muestras. La recolección de las muestras dura de unos 20 a 30 minutos.

Además, este consentimiento da permiso al investigador para obtener una copia del informe de patología del tejido pulmonar de usted que su médico envía a patología para el diagnóstico. Estos informes no se enviarán con ninguna información sobre su identificación personal.

PRUEBAS ADICIONALES A SU MUESTRA: En el futuro debido al descubrimiento de nuevos conocimientos a través de investigaciones y avances en técnicas en el campo del análisis genético, el investigador puede hacer otros análisis biológicos y genéticos enfocados solamente en la susceptibilidad al cáncer de pulmón y a otras enfermedades pulmonares causadas por las toxinas exhaladas u otras sustancias. Esto da consentimiento para realizar posibles análisis posteriores a sus muestras. Los análisis adicionales se enfocarán en los genes de procesamiento de compuestos extraños, genes relacionados con el cáncer y otros genes, marcadores proteínicos y biológicos relacionados con el metabolismo de sustancias extrañas, función celular y otros fenómenos relevantes a la enfermedad pulmonar. Se mantendrán todas las garantías mencionadas anteriormente para su confidencialidad. No estarán disponibles para usted los resultados de todos los análisis genéticos. Si usted desea hablar con un consejero genético sobre información general relacionada al almacenamiento de las muestras genéticas, puede llamar a un consejero genético.

Como usted no sabe el efecto de estos análisis, nosotros no revelaremos los resultados de los análisis genéticos. No se ofrecerá consejería oficial para este estudio de investigación. Si usted pide consejería, se le referirá a un consejero genético. Usted o su compañía de seguro médico serán responsables de los costos del consejero genético.

¿INVOLUCRARÁ ESTE ESTUDIO INVESTIGACIÓN GENÉTICA y/o ANÁLISIS GENÉTICOS?

Este estudio de investigación está diseñado para la exploración de genes y moléculas que pueden ser responsables de la susceptibilidad y/o desarrollo de la enfermedad pulmonar anticipándose al

establecimiento de las estrategias de detección molecular para la detección temprana de las enfermedades pulmonares, incluyendo el cáncer.

- Las pruebas que se realicen para este estudio de investigación pueden revelar información genética.
- **INFORMACIÓN SOBRE CONSEJERÍA GENÉTICA:** Usted puede querer consejería genética antes de firmar el consentimiento informado. Un consejero genético es una persona calificada para dar información sobre lo que pueden significar los resultados de este tipo de análisis para usted y su familia. Usted o su compañía de seguro serán responsables de los costos de estos servicios.

¿CUÁLES SON LOS POSIBLES EFECTOS SECUNDARIOS, MOLESTIAS, RIESGOS O INCONVENIENTES QUE PUEDO ESPERAR AL PARTICIPAR EN ESTE ESTUDIO DE INVESTIGACIÓN?

Aquí hay una lista de los riesgos conocidos relacionados con esta investigación:

- **Cuestionario:** Algunas veces, el hablar sobre el historial del tabaquismo o la exposición a contaminantes ambientales durante la entrevista puede producirle ansiedad.
- **Sangre:** Raras veces, se necesita un pinchazo adicional para recolectar muestras de sangre. Los riesgos involucrados en la obtención de la muestra de sangre son infección (poco frecuente), y moretón y dolor (a veces).
- **Boca:** Los hisopos con cepillos suaves raras veces causan molestias y sangrado. La solución de enjuague bucal causa una sensación de cosquilleo que desaparece rápidamente y en raras ocasiones causa molestia.
- **Condensado de aire exhalado:** La recolección del condensado de aire exhalado es una prueba no invasiva y no tiene ningún riesgo conocido. Usted puede sentir incomodidad al respirar en un tubo y posiblemente usar una pinza nasal de 10 a 15 minutos.
- **Saliva:** La recolección de la saliva no tiene ningún riesgo conocido.
- **Espujo:** El riesgo relacionado con la provocación del espujo incluye tos, disminución del nivel de oxígeno en la sangre, y broncoespasmos (estrechez de las vías respiratorias) en especial en personas con asma.

¿AFECTARÁN LOS RESULTADOS DE ESTE ESTUDIO O CUALQUIERA DE LOS PROCEDIMIENTOS LA OBTENCIÓN DE SEGURO MÉDICO?

Las pruebas que se realizan para este estudio no afectarán su capacidad obtener o conservar su seguro médico, seguro de salud o seguro de vida.

¿ES POSIBLE QUE HAYA ALGÚN BENEFICIO AL PARTICIPAR EN ESTE ESTUDIO DE INVESTIGACIÓN?

Usted no se beneficiará al participar en este estudio de investigación. Sin embargo, puede haber un beneficio general para la sociedad al fomentar el conocimiento científico. La información que se obtenga del uso de sus tejidos nos ayudará a entender mejor la enfermedad pulmonar y nos

ayudará a establecer las estrategias de detección molecular para la detección temprana de la enfermedad pulmonar y el cáncer de pulmón.

¿QUÉ OTRAS OPCIONES TENGO SI NO PARTICIPO EN ESTE ESTUDIO DE INVESTIGACIÓN?

- Usted puede elegir no participar en este estudio.

¿ME PAGARÁN POR PARTICIPAR EN EL ESTUDIO?

- Si decide participar en este estudio de investigación, le recompensaremos por su tiempo y sus gastos (\$5.00 por cada una de las 6 pruebas de laboratorio tal como se resume en la sección de procedimiento por una cantidad máxima de \$30.00).
Si no completa el estudio, su pago será de manera proporcional (pago relativo). Le pediremos su número de seguro social para poder procesar su pago.

¿QUIÉNES PUEDEN VER MIS REGISTROS?

- Los registros de la investigación se mantendrán confidenciales y su nombre no se usará en ningún informe escrito o verbal.
- Sus registros de la investigación y sus expedientes médicos pueden ser examinados por los miembros del equipo de investigación y otras instituciones que participan en este estudio. Estas instituciones son: la Administración de Alimentos y Medicamentos de los Estados Unidos (*U.S. Food and Drug Administration, FDA*), los Institutos Nacionales de la Salud (*National Institutes of Health, NIH*), las oficinas del Departamento de Salud y Servicios Humanos (*Department of Health and Human Services, DHHS*), el Departamento de Salud del Estado de Nueva York (*New York State Department of Health, NYSDOH*), las agencias gubernamentales en otros países, las agencias federales involucradas en la investigación, las agencias gubernamentales a las que se deben informar ciertas enfermedades (enfermedades de declaración obligatoria).
- El investigador y el personal de la investigación examinarán sus expedientes médicos y mantendrán la información confidencial.
- Los registros de la investigación se guardarán de manera segura y los registros computarizados se protegerán con una contraseña.
- Las personas que examinaron este estudio de investigación como miembros del Comité de Investigaciones Clínicas (*Committee on Clinical Investigations, CCI*) de la Escuela de Medicina Albert Einstein y de la Junta de Revisión Institucional (*Institutional Review Board, IRB*) del Centro Médico Montefiore también pueden examinar sus registros de la investigación y sus expedientes médicos.
- La Oficina para la Protección de los Seres Humanos en la Investigación (*Office for Human Research Protections, OHRP*) también puede examinar sus registros del estudio de investigación.
- Los registros de la investigación se guardarán de manera segura y los registros computarizados se protegerán con una contraseña en el Centro de Investigaciones Clínicas (*Clinical Research Center, CRC*) de la Escuela de Medicina Albert Einstein.

- El personal del Centro de Investigaciones Clínicas, así como el personal de la investigación autorizado por el investigador tendrán acceso a estos registros.
- A todos estos grupos se les ha pedido mantener su nombre de manera confidencial.

¿QUÉ PASA SI ME LESIONO PORQUE PARTICIPÉ EN ESTE ESTUDIO DE INVESTIGACIÓN?

Si tiene alguna lesión física como resultado de esta investigación, el hospital participante solamente le proveerá tratamiento médico inmediato, esencial, y a corto plazo para la lesión, libre de costo para usted.

- No se le ofrecerá ninguna compensación monetaria.
- Usted no renuncia a ninguno de sus derechos legales al firmar este consentimiento informado. Si se requiere tratamiento adicional como resultado de una lesión física relacionada con la investigación, se le proveerá tratamiento médico necesario y la factura se enviará a su compañía de seguro o a usted como parte de sus gastos médicos.
- Informe de inmediato cualquier molestia, dolencia o lesión que presente durante el curso de su participación en el estudio al Dr. Simon Spivack llamando al número 718-678-1040 de 9 a.m. a 5 p.m.

¿HABRÁ ALGÚN COSTO PARA MÍ?

- No habrá ningún costo para usted por participar en este estudio.

¿Se me puede pedir que deje de participar en este estudio antes de que el estudio termine?

- Si se alcanza la meta del estudio, podemos pedirle que deje de participar en este estudio.

¿QUIÉN PUEDE RESPONDER A MIS PREGUNTAS SOBRE EL ESTUDIO?

Nombre del investigador: *Dr. Simon Spivack*

Dirección de oficina: 1301 Morris Park Avenue, Price Center 268 Bronx, NY 10467

Número de teléfono: 718-678-1040

- Si tiene alguna pregunta relacionada con este proyecto de investigación, o cree que tiene alguna lesión relacionada con este estudio, puede llamar al investigador que se nombra arriba.
- Si tiene alguna pregunta sobre sus derechos como participante de la investigación, también puede llamar al jefe del Comité de Investigaciones Clínicas de la Escuela de Medicina Albert Einstein al número telefónico (718) 430-2253, de lunes a viernes de 9 a.m. a 5 p.m.

¿SE USARÁ ALGUNA DE LAS MUESTRAS (SANGRE, TEJIDO, ADN) QUE SE ME TOMARON PARA ESTUDIOS DE INVESTIGACIÓN FUTUROS?

FUTURAS INVESTIGACIONES A LAS MUESTRAS NO IDENTIFICADAS:

Introducción:

Además de la investigación a la que usted ha decidido participar por medio de este estudio de investigación, el Dr. Simon Spivack u otros investigadores en esta institución u otras instituciones, y agencias federales como el NIH, puede(n) querer estudiar las muestras en investigaciones futuras, entre ellas análisis genéticos. Estas muestras, que se tomaron de su cuerpo, durante esta cirugía médicamente necesaria que su médico ha recomendado **NO** serían relacionadas con usted. Nadie sabrá su nombre, ni sus iniciales (primera letra de su nombre y apellido), ni su fecha de nacimiento, ni su número de expediente médico, ni su número de seguro social ni otra información de identificación ni tampoco su información médica protegida. Por lo tanto, no se esperan riesgos adicionales de privacidad por compartir las muestras. Todos los nombres y otra información de identificación están bajo doble medida de seguridad y contraseña, las cuales están solo en manos del coordinador de la investigación, y no de los científicos. Sus muestras y datos se pueden usar para investigaciones futuras a pesar de que ahora el propósito de la investigación futura no se conoce. En este momento, el investigador no sabe cuáles serán los estudios futuros. Sus muestras y datos también se pueden enviar a un banco de tejido/células/ADN. Las muestras se pueden guardar durante mucho tiempo y pueden sobrepasar los 50 años.

En algunas investigaciones en las que se utilizan sangre o tejido humano, las muestras y los datos pueden permitir a los investigadores desarrollar pruebas médicas o tratamientos médicos que tengan valor comercial. Usted no recibirá ningún dinero que pueda resultar de alguna de tales pruebas comerciales o tratamientos.

FUTURAS PRUEBAS ESPECÍFICAS DE INVESTIGACIÓN A SU TEJIDO PULMONAR QUIRÚRGICO:

Como parte del análisis de cambios moleculares que provocan la aparición de cáncer de pulmón y de la respuesta al tratamiento, el tejido sobrante de la muestra de la biopsia de pulmón (si hay evidencia de tumor en el mismo) se implantará, con su autorización específica en una línea por separado que se indica abajo, en ratones de laboratorio para estudiar las características genéticas y evaluar varios agentes quimioterapéuticos y medicamentos contra el cáncer. Si acepta participar, este tejido quirúrgico se enviará del cirujano y del Departamento de Patología del Centro Médico Montefiore a los laboratorios de los doctores Edward Schwartz y Roman Perez-Soler y a sus asociados de investigación. Para permitir que se realice la mayor cantidad de investigaciones posible al tejido que done y aprender lo más posible, los investigadores de este estudio pueden compartir su tejido, sangre y ADN con otros científicos e investigadores en otras universidades, agencias y laboratorios gubernamentales, hospitales, compañías relacionadas con la salud, o institutos de investigación. Además, se pueden tomar algunas muestras para explorar el origen de las células madres en el laboratorio del Dr. Yakov Peter y sus colegas, nuevamente si tenemos su autorización específica en una línea por separado que se indica abajo.

Su participación en esta parte de la investigación es opcional. El alcance del procedimiento quirúrgico o la cantidad de tejido que se extrae no cambiarán como resultado de su participación en esta parte del estudio. Los investigadores usarán las muestras de tejido que, de otro modo, no se necesitan para el diagnóstico de su enfermedad.

El propósito de esta parte del estudio es examinar los diferentes cambios moleculares que ocurren en el cáncer de pulmón y correlacionar estos cambios con la respuesta a diferentes tratamientos contra el cáncer. Como parte del estudio, los coordinadores de la investigación que no tienen

acceso (esto es, «que se les oculta») a sus análisis genéticos examinarán su expediente médico para obtener la fase, el tipo de tumor, su edad, su grupo étnico, el tipo de tratamientos que ha recibido contra el cáncer y el resultado que incluye la supervivencia, si estuviera disponible. Esta información facilitará a los investigadores la ayuda para entender si hay alguna correlación entre lo que encontraron o lo que pusieron a prueba con el resultado actual de su cáncer.

Toda esta información clínica recogida por los coordinadores de la investigación se almacenará con un número de estudio. Nadie sabrá su nombre ni información médica protegida. Por eso, no se esperan riesgos adicionales de privacidad por recoger estos datos. Además, se puede hacer una evaluación similar en el futuro, ya sea de su expediente médico o del registro del cáncer para registrar el resultado o la supervivencia a su cáncer. Estos datos ayudan a los investigadores a analizar si una prueba médica que están estudiando pronostica el resultado bueno o malo a causa del cáncer.

Su información no identificada relacionada con su salud de su expediente médico se pondrá a disposición de los investigadores para evaluación, y se puede compartir con otros científicos e investigadores en otras universidades, agencias y laboratorios gubernamentales, hospitales, compañías relacionadas con la salud, o institutos de investigación.

*Los científicos que realizan la investigación no sabrán quién es usted. La información científica se almacenará con un número de estudio genérico asignado a usted que **no** se relaciona visiblemente con sus iniciales, fecha de nacimiento, número de expediente médico, número de seguro social u otra información de identificación. Los científicos solamente usarán/tendrán en cuenta este número, más no sus iniciales, fecha de nacimiento, número de expediente médico, número de seguro social u otra información de identificación. El coordinador de la investigación sabrá sus iniciales, fecha de nacimiento, número de seguro social u otra información de identificación, pero no sabrá los resultados de sus pruebas de investigación genéticas/de laboratorio. Por tal motivo, nadie tendrá el enlace de sus iniciales, fecha de nacimiento, número de expediente médico, número de seguro social u otra información de identificación y las pruebas de investigación genéticas/de laboratorio. Ningún investigador sabrá su nombre o información médica protegida. Esta «separación» de información le permite a usted permanecer de manera anónima al investigador.*

PROCEDIMIENTO: No hay procedimientos adicionales para esta parte del estudio. El tejido sobrante de la muestra de la biopsia, que no se necesite para diagnóstico o atención médica u otros fines de la investigación, se puede implantar en ratones para hacer pruebas moleculares adicionales y varios tratamientos contra el cáncer.

RIESGO: No hay riesgos adicionales por participar en esta parte del estudio. (a) El tejido que se va a poner a prueba ya se le habrá extraído de usted con el solo propósito de tratar su cáncer. (b) La posibilidad de pérdida de privacidad es algo muy mínimo debido a que: (i) separar la información de identificación de la información genética/de laboratorio previene que esta información se pueda reunir; (ii) información de identificación está doblemente protegida con una contraseña y está bajo llave por los coordinadores de la investigación; (iii) los investigadores científicos que están involucrados han hecho esto en más de 1 000 pacientes en este protocolo sin ninguna pérdida de privacidad; y (iv) esto es una estrategia habitual, ampliamente aceptada y usada a nivel nacional, en decenas de miles de participantes.

BENEFICIOS: Usted no se beneficiará por participar en esta parte del estudio de investigación. Sin embargo, la información que se aprenda de esta investigación puede, en el futuro, beneficiar a otras personas con la misma enfermedad. Los resultados de estas pruebas son para fines de investigación únicamente y **no** estarán disponibles para usted o su médico tratante.

PARTICIPANTE

POR FAVOR INDIQUE SU ELECCIÓN ESCRIBIENDO SUS INICIALES (PRIMERA LETRA DE SU NOMBRE Y APELLIDO) EN UNA (1) o MÁS DE LAS SIGUIENTES OPCIONES

_____ Doy mi consentimiento para que mis muestras se utilicen en todos los estudios de investigación futuros.

_____ Doy mi consentimiento para que mis muestras se utilicen en estudios de investigación futuros solamente para el estudio de

_____ Doy mi consentimiento para que mis muestras se implanten en ratones de laboratorio, y se almacenen y compartan con colaboradores en estudios futuros.

_____ Doy mi consentimiento para que mis muestras se utilicen para células madre pulmonares, en estudio futuros.

_____ **NO** doy mi consentimiento para que mis muestras se implanten en ratones de laboratorio para estudios futuros.

_____ **NO** doy mi consentimiento para que mis muestras se utilicen para células madre pulmonares en estudio futuros.

_____ **NO** doy mi consentimiento para que mis muestras se utilicen en ningún estudio de investigación futuro. (Las muestras serán destruidas al final del estudio actual).

¿QUÉ SUCEDERÁ SI INFORMACIÓN NUEVA SE HACE DISPONIBLE?

Si el doctor del estudio de investigación obtiene información nueva que pueda hacerle cambiar de opinión sobre continuar en este estudio, el doctor del estudio de investigación se lo informará. Si usted decide retirarse del estudio, el doctor del estudio de investigación y su doctor personal harán arreglos para que su atención médica continúe.

¿PUEDO DEJAR DE PARTICIPAR EN EL ESTUDIO EN CUALQUIER MOMENTO?

Su participación en este estudio es voluntaria, y puede dejar de participar en el estudio en cualquier momento sin tener que dar ninguna explicación.

Si acepta participar en el estudio y lo abandona después, parte de su información puede que ya se haya ingresado al estudio y eso no se podrá eliminar.

Además, a usted se le puede pedir que regrese a ver al doctor del estudio de investigación nuevamente para hacer cualquier prueba final, y así cerrar el registro y las pruebas o el monitoreo que son necesarios para su salud como resultado de su participación. Estos resultados se pueden registrar.

El tratamiento que recibe por parte de los doctores y del personal en la institución o las instituciones involucrada(s) en este estudio, no será afectado de ningún modo, ni ahora ni en el futuro, si usted acepta participar en este estudio y después lo abandona.

¿CUÁLES SON MIS DERECHOS SI PARTICIPO EN ESTE ESTUDIO DE INVESTIGACIÓN?

Su participación en este estudio es voluntaria.

Usted no renuncia a ninguno de sus derechos legales al participar en este estudio de investigación.

El tratamiento que usted recibe por parte de los doctores y del personal en la institución o las instituciones involucrada(s) en este estudio, no será afectado de ningún modo, ni ahora ni en el futuro, si usted se niega a participar en este estudio o si ingresa al estudio y después lo abandona.

Certificado de confidencialidad

Con el fin de proteger su privacidad, hemos obtenido un certificado de confidencialidad de los Institutos Nacionales de la Salud de los Estados Unidos (*National Institutes of Health*), que es la que financia este estudio. Si la información de este estudio fuera solicitada u ordenada por una orden judicial por las agencias del gobierno o las cortes, usaremos este certificado para legalmente negarnos a proporcionar tal información. Esto es una situación poco probable - solamente en unas pocas ocasiones, los investigadores tuvieron que usar el certificado, y se respetó la mayor parte del tiempo, pero no siempre. Existen varios tipos de situaciones en las que el certificado no es aplicable. Sin embargo, se nos exige, por ejemplo, denunciar abuso infantil y algunas enfermedades, y debemos poner a disposición del gobierno la información para un análisis o una evaluación de nuestra investigación. El certificado de confidencialidad no le impide a usted o a un familiar suyo compartir información de manera voluntaria. De manera similar, si una compañía de seguros, empleador u otra persona obtiene su autorización por escrito para recibir información sobre la investigación, entonces los investigadores no pueden usar el certificado de confidencialidad para no entregar esa información.

Página de firmas para la obtención del consentimiento informado

Lo siguiente es una lista de los temas del estudio de investigación sobre los cuales hemos hablado. Si usted tiene alguna pregunta sobre alguno de estos temas, por favor pídale a la persona con la que está hablando sobre el estudio que le dé más información antes de aceptar participar en el estudio.

- De qué trata el estudio.
- Qué debo hacer cuando esté en el estudio.
- Los posibles riesgos y beneficios para mí.
- A quién contactar si tengo preguntas o si hay alguna lesión relacionada con el estudio.
- Información sobre costos y pagos.
- Puedo dejar de participar en el estudio en cualquier momento sin recibir ninguna sanción.
- Información sobre otras opciones.
- Toda información escrita y publicada se informará como datos grupales y no se hará mención a mi nombre.

- Me han dado el nombre del investigador y de otros para contactarlos.
- Tengo el derecho de preguntar cualquier duda.

Nombre en letra de imprenta del
participante

Firma del participante

Fecha

Nombre en letra de imprenta de la
persona que lleva a cabo el proceso
del consentimiento informado

Firma de la persona que lleva a
cabo el proceso del consentimiento
informado

Fecha

Nombre del intérprete

Firma del intérprete

Fecha

**ALBERT EINSTEIN COLLEGE OF MEDICINE
MONTEFIORE MEDICAL CENTER**

Individual Information and Consent Form, Group 2 Bronchoscopy

You are being asked to join this research study.

The title of the study is: Genetics of Lung Disease (Exhaled Breath Markers in Lung Carcinogenesis)

The study is being done under the supervision of:

Principal Investigator (Researcher Study Doctor): Simon Spivack M.D.

Office Address: 1301 Morris Park Avenue, Price Center Rm 268 Bronx, NY 10467

Telephone #: 718 678-1040

Protocol #: 2007-407-000

Funded by: National Institute of Health and Department of Defense.

DO I HAVE TO TAKE PART IN THIS RESEARCH STUDY?

Your participation is voluntary. This means that you decide whether or not you want to join the study after speaking with the researcher, or other member of the research team. If you decide to take part you will be asked to sign this consent form. Your signature means that you agree to be a subject in this research.

After reading this form and having a discussion about what it says, you should ask all the questions you want to ask. You should take as much time as you need to make a decision.

If you do not understand some of the terms used in this form, ask the person who is discussing the study with you to give any additional information that may make this easier to understand.

You do not have to consent to participate in the study immediately, or ever. Take time to decide whether or not you wish to join. You may take home a copy of this consent form to think about it or discuss the information with family or friends before you decide.

If you decide not to participate, the care providers at this facility will give you all of the standard care that is appropriate for you.

You will be given a copy of this form whether or not you agree to participate in this study. Do not sign the form unless you have had all your questions answered and understand exactly what is involved.

If you decide to take part you are still free to withdraw at any time without giving a reason. This will not affect your care and you will continue to be treated at this facility.

The form discusses:

WHAT THE RESEARCHERS WILL LEARN FROM THE RESEARCH

WHAT WILL HAPPEN TO YOU DURING THE RESEARCH

WHAT RISKS AND/OR DISCOMFORTS YOU MIGHT EXPECT/EXPERIENCE AS A RESEARCH SUBJECT

IF YOU CAN EXPECT ANY BENEFITS, AND ARE THERE ANY ALTERNATIVES TO THIS RESEARCH FOR YOUR CONDITION.

WHY HAVE I BEEN ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being asked to take part in a research study because you will soon be having a bronchoscopy for a clinical reason (your medical care) .

WHY IS THIS RESEARCH STUDY BEING DONE?

This research will attempt to establish a relationship between the molecular changes that occur in cells from the mouth, saliva, sputum, exhaled breath and blood as they relate to the development of lung disease. If this relationship can be proven, it may be possible in the future to test for certain lung disease with a simpler laboratory test.

Dr. Simon Spivack, the principal investigator, is conducting a research investigation to determine whether the activity of certain genes and proteins in the lung and other tissues increases with exposure to cigarette smoke or environmental hazards. This increased activity might impact the development of lung disease. Genes instruct proteins to control and direct many activities of cells in the human body. The genes of interest to this investigation include inhaled foreign compound-processing genes, certain cancer-associated genes, and other genes, proteins and biological markers associated with the metabolism of foreign substances, cellular function, and other lung disease-related processes. The activity of genes and proteins found in the lung are thought to possibly parallel that detected in blood, saliva, exhaled breath condensate (moisture) and mouth cells. This is unproven. Additionally, the relationship of these genes' activity to lung diseases, including lung cancer, remains unproven.

Also the causes of discordance between the rare development of upper airway/laryngeal cancers versus the ten-fold more common development of lung cancers in smokers remains unclear. By this study we wish to perform an intra-individual molecular comparison of the two anatomic airway sites. Such host resistance factors in the upper airway might serve to enlighten the path to lower airway/ lung cancer prevention.

HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

You will be one of approximately 2000 who will be participating in this study at Montefiore Medical Center and Albert Einstein College of Medicine.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

If you agree, we will tell you more about the study and answer any questions you may have before your bronchoscopy procedure.

We expect that you will be in this research study from the time informed consent is signed until you complete your bronchoscopy.

The interview process and specimen collection takes approximately 40 minutes,

PROCEDURES:

Bronchoscopy procedure: With your consent, and with the approval of the physician performing the bronchoscopy, we would like to perform standard and fluoroscopic bronchoscopy and several additional collections. First, a bronchoalveolar lavage (BAL) will be performed. A BAL is a procedure done during the bronchoscopy when five 20cc aliquots (each 20cc aliquot is equal to 4 teaspoons, equalling 20 teaspoons total) of sterile salt water fluid is inserted into a small part of the lung and partially collected for examination. Second, the bronchoscopist will be taking six additional very small biopsy specimens, using fine tweezers (forceps) or small brushes. The forceps biopsies (removal of a small amount of upper/lower airway tissue) are each smaller than the point on the tip of a pencil; the other is by the use of small brushes. The small tweezers/brushes are inserted through the bronchoscope. With your consent, your physician will use a brush to collect tiny samples of larynx and lung tissue. These two types of airway tissue samples and/or fluid from BAL will be compared to the blood, sputum, exhaled breath, and other cells you may have donated. Analysis of the lung genes (DNA) or their products (RNA, proteins, metabolites), will be performed by examining these small portions of lung tissue removed by your surgeon or pulmonologist during bronchoscopy. Each of these additional procedures will lengthen the time of your bronchoscopy procedure by a few minutes.

If you agree to participate, this surgical tissue will be forwarded from the surgeon and Department of Pathology at Montefiore Medical Center to Dr. Spivack and his research associates at the laboratory in the Price Center, Albert Einstein College of Medicine, Bronx, NY.

You will be asked to complete a questionnaire regarding the amount you have smoked, your diet, other environmental exposures, medication and family history. This information is crucial to this study. The questionnaire will be administered by research nurse study staff and takes about 15 minutes to complete.

There are six (6) noninvasive specimens study staff would like to collect:

- Extra tubes of blood (30 mls or about 2 tablespoons of blood) will be drawn at the same time as your clinically indicated pre-anesthesia blood tests or at the same time your IV is inserted prior to your bronchoscopy, to avoid extra needle sticks.
- A collection of mouth cells by rinsing your mouth with an over-the-counter mouthwash solution.
- A manual spinning soft brush will be held against the lining of each cheeks four times to collect additional mouth cells.
- A collection of your exhaled breath condensate (EBC). This will be done by having you rinse your mouth with water and then breathing normally into a disposable portable mouthpiece for 10-15 minutes to collect 1 ml (less than one quarter teaspoon) of EBC. It may be necessary to wear a nose clip during the collection.
- A collection of your saliva, by spitting into a cup. A second collection of your saliva, obtained by chewing on a cotton-wool swab called a salivette for about 30 to 60 seconds, will be obtained. One can measure cotinine, reflective on smoking, in the saliva, in addition to other measurements.

- A collection of your sputum (phlegm from your throat) will be collected by taking a deep breath and coughing sputum directly into a collection cup. If you are unable to collect sputum this way we may give you a saline nebulizer for 10 minutes to moisten the airway and then ask you to take a deep breath and cough sputum directly into a collection cup.

The six non-invasive specimens are collected by research staff or phlebotomy staff. Specimen collection takes about 20-30 minutes.

In addition, this consent gives permission to the investigator to obtain a copy of the pathology report for your lung tissue that is sent by your physician to pathology for diagnosis. These reports will not be sent with any information regarding your personal identity.

ADDITIONAL TESTS ON YOUR SAMPLE: In the future because of the acquisition of new knowledge through research and advances in techniques in the field of genetic testing, the investigator may wish to conduct other biologic and genetic testing focused solely on the susceptibility to lung cancer and other lung diseases caused by inhaled toxins, or other substances. This gives consent for possible further testing on your specimens. The additional tests would be focused on foreign compound-processing genes, cancer-associated genes and other genes, proteins and biologic markers associated with the metabolism of foreign substances, cellular function, and other lung disease-relevant phenomena. All previously mentioned assurances for your confidentiality will be maintained. The results of all genetic testing will not be made available to you. If you would like to speak with a genetics counselor about general information concerning the storage of genetic specimens, you may call one.

Since the significance of these tests are not known for you, we will not disclose the results of the genetic testing. No formal counseling will be provided under the research study. If you request, you will be referred to a genetic counselor. You or your insurance carrier will be responsible for the genetic counselor's fee.

WILL THIS STUDY INVOLVE GENETIC RESEARCH and/or TESTING?

This research study is designed to explore the genes and molecules that may be responsible for the susceptibility and/or development of lung disease in anticipation of establishing molecular screening strategies for the early detection of lung diseases, including cancer.

Tests conducted under this research study may reveal genetic information.

GENETIC COUNSELING INFORMATION: You may wish to obtain professional genetic counseling prior to signing the informed consent. A genetic counselor is a person qualified to provide information about what the results of this type of test may mean to you and your family. You or your insurance company will be responsible for the cost of these services.

WHAT ARE THE POSSIBLE SIDE EFFECTS, DISCOMFORTS, RISKS OR INCONVENIENCES I CAN EXPECT FROM BEING IN THIS RESEARCH STUDY?

Here is a list of the known risks associated with this research:

Questionnaire: Occasionally, the discussion about smoking history or environmental contaminant exposure during the interview process may provoke anxiety.

Blood: Rarely, is an extra needle stick required to collect the blood specimens. The risks involved in blood sampling are infection (rare) and bruising and pain (occasionally).

Mouth: swabs with soft brushes rarely may cause discomfort and bleeding. The mouthwash solution causes a tingling sensation that resolves quickly and rarely is a cause for discomfort.

Exhaled breath condensate: collection is a non-invasive test and does not have any known risk. You may feel uncomfortable from breathing into a tube and possibly wearing a nose clip for 10-15 minutes.

–Saliva: collection does not have any known risk.

Sputum: The risk regarding the sputum induction include cough, fall in oxygen level in the blood, and bronchospasm (narrowing of the airway) especially in asthmatics.

BRONCHOSCOPY RISK:

Extra Procedures in Bronchoscopy:

For patients who have consented to have biopsies not needed for their clinical diagnosis, the incidence of minor to moderate bleeding is small (3 in 1000) and usually resolves spontaneously within minutes. The risk of increased bleeding that would require non-surgical treatment (medication called epinephrine will be applied topically to stop bleeding) is even smaller (less than 1 in 1000). The incidence of collapsed lung from endobronchial biopsy, requiring chest tube insertion to be placed to reinflate the lung, is expected to be much less than the 3 in 1000 estimated for transbronchial biopsies, because the procedure is performed under direct visual guidance.

For patients having bronchoalveolar lavage (BAL), there are no additional risks in up to 95% (95 in 100) of patients. Of the remaining ~5% (5 in 100), most complications are minor, and very brief, including transient (lasting seconds-minutes) decrease in baseline blood oxygen (frequency approximately 2 in 100), fever of short duration (approximately 2 in 100), cough (approximately 1 in 100), chills of short duration (less than 1 in 100), bronchospasm (narrowing of the airway, in less than 1 in 100). Bronchospasm treatment includes supplemental oxygen and an inhaled aerosol medication given by nebulizer. Brushing the inside of the larynx (voice box) could cause minor sore throat (estimated 5 in 100) after the procedure.

Life-threatening bronchoscopy procedure complications occur very rarely, estimated as less than 1 in 10,000. These bronchoscopy procedures may be uncomfortable and may extend (take a little longer to complete) the bronchoscopy (approximately 4-8 minutes), possibly requiring additional sedatives (medicine to help keep you comfortable).

Fluorescence bronchoscopy prolongs procedure duration for 5-8 minutes, there are no known additional risks.

WILL THE RESULTS OF THIS STUDY OR ANY OF THE PROCEDURES AFFECT MY INSURABILITY?

The tests done under this study will not affect your ability to get or keep medical, health or life insurance.

ARE THERE LIKELY TO BE ANY BENEFITS TO TAKING PART IN THIS RESEARCH STUDY?

You will not benefit from being in this research study. However, there may be a general benefit to society by the furthering of scientific knowledge. The information gained by using your tissues will help us better understand lung disease and help us establish molecular screening strategies for the early detection of lung disease and lung cancer.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS RESEARCH STUDY?

—You may choose not to participate in this study, in part or in whole.

WILL I BE PAID FOR BEING IN THE STUDY?

If you agree to take part in this research study, we will compensate (give) you for your time and expenses (\$5.00 each for 6 lab tests as outlined in procedure section and \$45.00 for bronchoscopy procedure for maximum amount of \$75.00) .

If you do not complete the study, your payment will be prorated (adjusted). We will be collecting your social security number in order to process your payment.

WHO MAY SEE MY RECORDS?

The research records will be kept private and your name will not be used in any written or verbal reports.

Your research records and medical records may be inspected by members of the research team and other institutions that participate in this study. These are: The U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), Department of defense (DoD)research monitors. Department of Health and Human Services (DHHS) offices, Governmental agencies in other countries, Federal agencies involved with research, governmental agencies to whom certain diseases (reportable diseases) must be reported. The researcher and research staff will review your medical records and will keep the information private.

The research records will be kept in a secured manner and computer records will be password protected.

The people who reviewed this research study as members of the Albert Einstein College of Medicine Committee on Clinical Investigations (CCI) and the Montefiore Medical Center Institutional Review Board (IRB) may also review your research and medical records.

The Office of Human Research Protections (OHRP) may also review your research study records.

The research records will be kept in a secured manner and computer records will be password protected in the Albert Einstein College of Medicine Clinical Research Center (CRC).

The Clinical Research Center staff, as well as the research personnel authorized by the researcher will have access to these records.

All of these groups have been requested to keep your name private.

Certificate of Confidentiality

As a way to protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health, which is funding this study. If information from this study was requested or subpoenaed by government agencies or the courts, we will use the Certificate to attempt to legally refuse to provide it. This is rare – in only a few cases did researchers have to use the Certificate, and it was honored most of the time, but not every time. There are several kinds of situations that the Certificate does not apply. For example, we are still required to report child abuse and some diseases, and we must make data available to the government for a review or evaluation of our research. The Certificate does not prevent you or a member of your family from voluntarily sharing information. Similarly, if an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

If there is a physical injury as a result of this research, only immediate, essential, short-term medical treatment as determined by the participating hospital, will be available for the injury without charge to you personally.

No monetary compensation will be offered.

You are not waiving any of your legal rights by signing this informed consent document

If additional treatment is required as a result of a physical injury related to the research, necessary medical treatment will be provided to you and billed to your insurance company or to you as part of your medical expenses.

Immediately report any discomforts, problems or injuries you experience during the course of your participation in the study to Dr. Simon Spivack at 718 678-1040 between the hours of 9am to 5pm.

WILL THERE BE ANY COSTS TO ME?

There will be no costs to you for participating in this study.

Can I be asked to stop participating in this study before the study is finished?

If the study goal has been reached, you can be asked to stop participating.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

Researcher's Name: Dr. Simon Spivack

Office Address: 1301 Morris Park Avenue Price Center 268Bronx, NY 10467

Office Phone: 718-678-1040

If any questions arise related to this research project, or you believe you have any injury related to this study, you can call the researcher above.

If you have questions regarding your rights as a research subject, you may also call the Manager of The Albert Einstein College of Medicine Committee on Clinical Investigations at (718) 430-2253, Monday through Friday between 9 AM and 5 PM.

WILL ANY OF THE SAMPLES (BLOOD, TISSUE, DNA) TAKEN FROM ME BE USED FOR FUTURE RESEARCH STUDIES?

USE OF DE-IDENTIFIED SPECIMENS FOR FUTURE RESEARCH:

In addition to the research you are consenting to under this research study, Dr. Simon Spivack or other researchers at this or other institutions may wish to study the samples in future research, including genetic analysis. These samples, taken from your body, would NOT be linked back to you. No one will know your name or protected health information.

At this time, the researcher does not know what the future studies will be. Your specimens may also be submitted to a tissue/cell/DNA bank. The specimens may be kept for a long time and may exceed 50 years.

In some research using human blood or tissue, the specimens and their parts may enable researchers to develop medical tests or treatments that have commercial value. You will not receive any money that may result from any such commercial tests or treatments.

Your specimens may be used for future research, even though the purpose of the future research is not known at this time.

PARTICIPANT:

PLEASE INDICATE YOUR CHOICE BY INITIALING ONE (1) OF THE FOLLOWING OPTIONS

I consent to have my specimens used for future research studies.

I consent to have my specimens used for future research studies only for the study of _____.

I do NOT consent to have my specimens used for future research studies. (The specimens will be destroyed at the end of the study.)

WHAT IF NEW INFORMATION BECOMES AVAILABLE?

If the research study doctor obtains new information that might lead you to change your mind about continuing in this study, the research study doctor will tell you about it.

If you decide to withdraw, the research study doctor and your personal doctor will make arrangements for your care to continue.

MAY I STOP THE STUDY AT ANY TIME?

Your participation in this study is voluntary, and you may withdraw from the study at any time without giving a reason.

If you agree to participate and withdraw at a later time, some of your information may have already been entered into the study and that will not be removed.

In addition, you may be asked to return to the research study doctor again for any final tests in order to close the record and tests or monitoring that are necessary for your health as a result of your participation. These results may be recorded.

Your treatment by doctors and staff at the institution(s) involved in this study, now and in the future, will not be affected in any way if you agree to participate and withdraw later.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS RESEARCH STUDY?

Your participation in this study is voluntary.

You do not waive any of your legal rights by participating in this research study.

Your treatment by doctors and staff at the institution(s) involved in this study, now and in the future, will not be affected in any way if you refuse to participate or if you enter the study and withdraw later.

Informed Consent Signature Page

The following is a list of items we discussed about this research study. If you have any questions about any of these items, please ask the person who is discussing the study with you for more information before agreeing to participate.

What the study is about.

What I must do when I am in the study.

The possible risks and benefits to me.

Who to contact if I have questions or if there is a research related injury.

Any costs and payments.

I can discontinue participating in the study at any time without penalty.

Other choices.

All written and published information will be reported as group data with no reference to my name.

I have been given the name of the researcher and others to contact.

I have the right to ask any questions.

Printed Name of Participant

Signature of Participant

Date

Printed Name of Person Conducting the
Informed Consent Process

Signature of Person Conducting the
Informed Consent Process

Date

**ALBERT EINSTEIN COLLEGE OF MEDICINE OF YESHIVA UNIVERSITY
MONTEFIORE MEDICAL CENTER**

Información para el participante y formulario de consentimiento

Grupo 2, Broncoscopia

Se le está pidiendo que participe en este estudio de investigación.

El nombre del estudio es: Genética de la enfermedad pulmonar (marcadores en aire exhalado en la carcinogénesis pulmonar)

El estudio se está llevando a cabo bajo la supervisión de:

Investigador principal (doctor del estudio de investigación): Simon Spivack, MD
Dirección de oficina: 1301 Morris Park Avenue, Price Center Rm 268 Bronx, NY 10467
Número de teléfono: 718-678-1040
Número de protocolo: 2007-407-000

Declaración: El investigador principal, Dr. Simon Spivack, ha recibido una patente de una forma específica de analizar la metilación (cambios) del ADN que se llama GC (guanina y citosina) etiquetada con la secuenciación genómica de bisulfito. Este método se está usando en el estudio actual. En base a los datos de ésta y otras investigaciones, puede ser que el posible valor económico de este método de prueba aumente. De esta manera, la institución y el investigador principal tienen un posible interés económico en el resultado de este estudio.

¿TENGO QUE PARTICIPAR EN ESTE ESTUDIO DE INVESTIGACIÓN?

- Su participación es voluntaria. Esto quiere decir que usted decide si quiere participar el estudio o no después de hablar con el investigador, u otro miembro del equipo de investigación.
- Si decide participar en el estudio, le pediremos que firme este formulario de consentimiento. Su firma significa que usted acepta ser participante en esta investigación.
- Después de que usted lea este formulario y haya hablado sobre lo que trata el formulario, usted debe preguntar todo lo que quiere saber. Debe tomarse el tiempo que necesite antes de tomar una decisión.
- Si no entiende algunas de las palabras que se usan en este formulario, pídale a la persona con la que usted está hablando sobre el estudio que le dé información adicional que le permita entender más fácilmente.
- Usted no tiene que aceptar participar en el estudio ahora o en el futuro. Tómese su tiempo para decidir si desea participar o no. Usted puede llevarse una copia de este formulario de consentimiento para que lo piense o pueda comentar la información a su familia o sus amistades antes de tomar una decisión.
- Si usted decide no participar, los proveedores de atención médica en este centro le brindarán toda la atención médica habitual apropiada para usted.
- A usted se le dará una copia de este formulario, ya sea si acepta participar o no en este estudio. No firme el formulario a menos que le hayamos respondido a todas sus preguntas y entienda exactamente de lo que trata el estudio.
- Si decide participar en el estudio, todavía tiene la libertad de retirarse del estudio en cualquier momento sin tener que dar ninguna explicación. El retirarse del estudio no afectará su atención médica y usted continuará su tratamiento en este centro.

- El formulario trata sobre:
 - LO QUE LOS INVESTIGADORES SABRÁN DE LA INVESTIGACIÓN.
 - LO QUE LE PASARÁ A USTED DURANTE LA INVESTIGACIÓN.
 - LOS RIESGOS Y/O LAS MOLESTIAS QUE PUEDE ESPERAR/PRESENTAR COMO PARTICIPANTE DE LA INVESTIGACIÓN.
 - SI USTED PUEDE RECIBIR ALGÚN BENEFICIO, Y SI ¿HAY ALGUNA ALTERNATIVA A ESTA INVESTIGACIÓN PARA SU ENFERMEDAD?

¿POR QUÉ ME HAN PEDIDO QUE PARTICIPE EN ESTE ESTUDIO DE INVESTIGACIÓN?

Le estamos pidiendo que participe en el estudio de investigación porque pronto usted tendrá una broncoscopia por un motivo clínico (su atención médica).

¿POR QUÉ SE ESTÁ HACIENDO ESTE ESTUDIO DE INVESTIGACIÓN?

- Esta investigación tratará de establecer la relación entre los cambios moleculares que ocurren en las células de la boca, la saliva, el esputo, el aire exhalado y la sangre en relación al desarrollo de la enfermedad pulmonar. Si esta relación se puede probar, puede ser posible que en el futuro se hagan pruebas para detectar cierta enfermedad pulmonar con una prueba de laboratorio más simple.
- El Dr. Simon Spivack, el investigador principal, es el que está llevando a cabo la investigación para determinar si la actividad de ciertos genes y proteínas en el pulmón y en otros tejidos aumenta con la exposición al humo del cigarrillo o a los peligros ambientales. El incremento de esta actividad puede tener un efecto en el desarrollo de la enfermedad pulmonar. Los genes ordenan a las proteínas a controlar y dirigir muchas actividades de las células en el cuerpo humano. Los genes que son de interés para esta investigación incluyen los genes de procesamiento de compuestos extraños inhalados, ciertos genes relacionados con el cáncer y otros genes, marcadores proteínicos y biológicos relacionados con el metabolismo de sustancias extrañas, función celular y otros procesos relacionados con la enfermedad pulmonar. Se cree que la actividad de los genes y las proteínas encontradas en los pulmones son posiblemente iguales a aquella detectada en la sangre, la saliva, el condensado de aire exhalado (humedad) y las células de la boca. Esto no está probado. Además, la relación de la actividad de estos genes con las enfermedades pulmonares, incluyendo el cáncer de pulmón, continúa sin probarse.

¿CUÁNTAS PERSONAS PARTICIPARÁN EN ESTE ESTUDIO DE INVESTIGACIÓN?

Usted será una(o) de aproximadamente 2 000 personas que estarán participando en este estudio en el Centro Médico Montefiore (*Montefiore Medical Center*) y en la Escuela de Medicina Albert Einstein (*Albert Einstein College of Medicine*).

¿QUÉ SUCEDERÁ SI PARTICIPO EN ESTE ESTUDIO DE INVESTIGACIÓN?

Si usted decide participar, le diremos más sobre el estudio y responderemos cualquier pregunta que tenga antes de su procedimiento de broncoscopia.

Esperamos que usted participe en este estudio de investigación desde el momento que usted firme el consentimiento informado hasta que complete la broncoscopia.

El proceso de la entrevista y la recolección de muestras toman unos 40 minutos.

PROCEDIMIENTOS:

- Procedimiento de broncoscopia: Con su consentimiento, y con la aprobación del médico que realiza la broncoscopia, desearíamos hacer una broncoscopia estándar y fluoroscópica, y varias recolecciones adicionales. Primero, se le hará un lavado broncoalveolar (LBA). El lavado broncoalveolar es un procedimiento que se hace durante la broncoscopia cuando cinco alícuotas de 20 cc (cada alícuota de 20 cc es igual a 4 cucharaditas, equivalente a un total de 20 cucharaditas) de solución de agua salina estéril se introduce en una parte pequeña del pulmón y se recolecta parcialmente para su análisis. Segundo, el especialista en broncoscopia tomará cuatro muestras adicionales de biopsia muy pequeñas usando pinzas (tenacillas) finas o cepillitos. Las pinzas de biopsia (la extracción de una pequeña cantidad de tejido pulmonar) son cada una más pequeña que la punta de un lápiz. El otro método para recoger el tejido pulmonar durante la broncoscopia es mediante el uso de unos cepillos pequeños. Las pinzas/cepillos pequeños se introducen a través del broncoscopio. Con su consentimiento, su médico usará un cepillo para recolectar una muestra muy pequeña de tejido pulmonar. Este tejido pulmonar y/o líquidos del lavado broncoalveolar se compararán con la sangre, el esputo, y otras células que usted pueda haber donado. Los análisis de los genes pulmonares (ADN) o de sus productos (ARN y proteínas) se harán examinando estas pequeñas porciones de tejido pulmonar que su cirujano o pulmonólogo extirpó durante la broncoscopia. Cada uno de estos procedimientos adicionales aumentarán el tiempo del procedimiento de la broncoscopia. Si acepta participar, este tejido quirúrgico se enviará del cirujano y del Departamento de Patología del Centro Médico Montefiore al Dr. Spivack y a sus asociados de investigación en el Centro Price (*Price Center*, por su nombre en inglés), en la Escuela de Medicina Albert Einstein, Bronx, NY.
- Le pediremos que complete un cuestionario sobre la cantidad de cigarrillos que ha fumado, los alimentos que come, otras exposiciones ambientales, medicamentos, y antecedentes familiares. Esta información es de suma importancia para este estudio.
- Un(a) enfermero(a) de investigación del personal del estudio le tomará el cuestionario y durará cerca de 15 minutos completarlo.
- El personal del estudio recolectará seis (6) muestras:
 - Se le extraerán tubitos adicionales de sangre (30 mililitros o unas 2 cucharadas de sangre) al mismo tiempo que se le hagan las pruebas de sangre preanestésicas por indicación clínica o al mismo tiempo que se le introduzca la vía intravenosa antes de la broncoscopia, para evitar pinchazos de agujas adicionales.
 - Se recolectarán células de la boca enjuagándose la boca con una solución de enjuague bucal que es sin receta médica.
 - Se recolectarán células de la boca adicionales sosteniendo cuatro veces un cepillo suave de uso manual contra el revestimiento de cada mejilla.
 - Se recolectará una muestra de condensado de aire exhalado (CAE). Esta muestra se le tomará por medio del enjuague de la boca con agua y luego respirará normalmente en una boquilla portátil descartable de 10 a 15 minutos para recolectar 1 mililitro (menos de un cuarto de cucharadita) de condensado de aire exhalado. Pueda que sea necesario usar una pinza nasal durante la recolección de la muestra.

- Se recolectará una muestra de su saliva, tendrá que escupir en un vasito. Se recolectará una segunda muestra de su saliva la cual se obtendrá masticando un hisopo de algodón que se llama salivette de 30 a 60 segundos. Uno puede medir la cotinina, que se refleja al fumar, en la saliva, aparte de otras medidas.
- Se recolectará una muestra de esputo (flema de la garganta). Respirará profundamente y toserá el esputo directamente en el vaso para la muestra. Si usted no puede recolectar el esputo de esta manera, podemos darle un nebulizador salino por 10 minutos para humedecer las vías respiratorias y luego le pediremos que respire profundamente y tosa el esputo directamente en el vaso para la muestra.

El personal de la investigación o el personal de flebotomía recolectarán las seis muestras.

La recolección de las muestras dura de unos 20 a 30 minutos.

Además, este consentimiento da permiso al investigador para obtener una copia del informe de patología del tejido pulmonar de usted que su médico envía a patología para el diagnóstico. Estos informes no se enviarán con ninguna información sobre su identificación personal.

- **PRUEBAS ADICIONALES A SU MUESTRA:** En el futuro debido al descubrimiento de nuevos conocimientos a través de investigaciones y avances en técnicas en el campo del análisis genético, el investigador puede querer hacer otros análisis biológicos y genéticos enfocados solamente en la susceptibilidad al cáncer de pulmón y a otras enfermedades pulmonares causadas por las toxinas exhaladas u otras sustancias. Esto da consentimiento para realizar posibles análisis posteriores a sus muestras. Los análisis adicionales se enfocarán en los genes de procesamiento de compuestos extraños, genes relacionados con el cáncer y otros genes, marcadores proteínicos y biológicos relacionados con el metabolismo de sustancias extrañas, función celular y otros fenómenos relevantes a la enfermedad pulmonar. Se mantendrán todas las garantías mencionadas anteriormente para su confidencialidad. No estarán disponibles para usted los resultados de todos los análisis genéticos. Si usted desea hablar con un consejero genético sobre información general relacionada al almacenamiento de las muestras genéticas, puede llamar a un consejero genético.
- Como usted no sabe el efecto de estos análisis, nosotros no revelaremos los resultados de los análisis genéticos. No se ofrecerá consejería oficial para este estudio de investigación. Si usted pide consejería, se le referirá a un consejero genético. Usted o su compañía de seguro médico serán responsables de los costos del consejero genético.

¿INVOLUCRARÁ ESTE ESTUDIO INVESTIGACIÓN GENÉTICA y/o ANÁLISIS GENÉTICOS?

Este estudio de investigación está diseñado para la exploración de genes y moléculas que pueden ser responsables de la susceptibilidad y/o desarrollo de la enfermedad pulmonar anticipándose al establecimiento de las estrategias de detección molecular para la detección temprana de las enfermedades pulmonares, incluyendo el cáncer.

- Las pruebas que se realicen para este estudio de investigación pueden revelar información genética.
- **INFORMACIÓN SOBRE CONSEJERÍA GENÉTICA:** Usted puede querer consejería genética antes de firmar el consentimiento informado. Un consejero genético es una persona calificada para dar información sobre lo que pueden significar los resultados de este tipo de

análisis para usted y su familia. Usted o su compañía de seguro serán responsables de los costos de estos servicios.

¿CUÁLES SON LOS POSIBLES EFECTOS SECUNDARIOS, MOLESTIAS, RIESGOS O INCONVENIENTES QUE PUEDO ESPERAR AL PARTICIPAR EN ESTE ESTUDIO DE INVESTIGACIÓN?

Aquí hay una lista de los riesgos conocidos relacionados con esta investigación:

- **Cuestionario:** Algunas veces, el hablar sobre el historial del tabaquismo o la exposición a contaminantes ambientales durante la entrevista puede producirle ansiedad.
- **Sangre:** Raras veces, se necesita un pinchazo adicional para recolectar muestras de sangre. Los riesgos involucrados en la obtención de la muestra de sangre son infección (poco frecuente), y moretón y dolor (a veces).
- **Boca:** Los hisopos con cepillos suaves raras veces causan molestias y sangrado. La solución de enjuague bucal causa una sensación de cosquilleo que desaparece rápidamente y en raras ocasiones causa molestia.
- **Condensado de aire exhalado:** La recolección del condensado de aire exhalado es una prueba no invasiva y no tiene ningún riesgo conocido. Usted puede sentir incomodidad al respirar en un tubo y posiblemente usar una pinza nasal de 10 a 15 minutos.
- **Saliva:** La recolección de la saliva no tiene ningún riesgo conocido.
- **Espujo:** El riesgo relacionado con la provocación del espujo incluye tos, disminución del nivel de oxígeno en la sangre, y broncoespasmos (estrechez de las vías respiratorias) en especial en personas con asma.

RIESGO DE LA BRONCOSCOPIA:

Procedimientos adicionales en la broncoscopia:

Para los pacientes que han dado su consentimiento para hacerse biopsias que no son necesarias para sus diagnósticos clínicos, la incidencia de sangrado leve a moderado es pequeña (3 de cada 1000), y por lo general se resuelve por sí solo en unos minutos. El riesgo del aumento del sangrado que necesitaría tratamiento no quirúrgico (medicamento llamado epinefrina se aplicará por vía tópica para parar el sangrado) es aún menor (menos de 1 de cada 1 000). La incidencia de pulmón colapsado a causa de la biopsia endobronquial, que requiere la inserción del tubo torácico para expandir el pulmón, se espera que sea mucho menor de 3 de cada 1 000 aproximado para las biopsias transbronquiales, porque el procedimiento se hace bajo guía visual directa.

Para los pacientes que se someten a un lavado broncoalveolar (LBA), no existen riesgos adicionales en hasta 95 % (95 de cada 100) de los pacientes. Del ~5 % restante (5 de cada 100), la mayoría de las complicaciones son leves y de corto tiempo, incluyendo descenso transitorio (que dura segundos-minutos) en los valores iniciales del oxígeno en la sangre (frecuencia aproximadamente 2 de cada 100), fiebre de corta duración (aproximadamente 2 de cada 100), tos (aproximadamente 1 de cada 100), escalofríos de corta duración (menos de 1 de cada 100), broncoespasmo (estrechez de las vías respiratorias, en menos de 1 de cada 100). El tratamiento para el broncoespasmo incluye oxígeno suplementario y un medicamento en aerosol por vía inhalatoria administrado a través de un nebulizador. Muy raras veces ocurren complicaciones potencialmente mortales, estimadas en menos de 1 de cada 10 000.

Estos procedimientos de broncoscopia pueden ser incómodos y pueden extender (tomar un poco más de tiempo para terminar) la broncoscopia (aproximadamente de 4 a 8 minutos), pueda que requiera sedantes adicionales (medicina que le ayuda a tener comodidad durante el procedimiento).

La broncoscopia fluorescente prolonga la duración del procedimiento de 5 a 8 minutos, no hay riesgos adicionales conocidos.

¿AFECTARÁN LOS RESULTADOS DE ESTE ESTUDIO O CUALQUIERA DE LOS PROCEDIMIENTOS LA OBTENCIÓN DE SEGURO MÉDICO?

Las pruebas que se realizan para este estudio no afectarán su capacidad obtener o conservar su seguro médico, seguro de salud o seguro de vida.

¿ES POSIBLE QUE HAYA ALGÚN BENEFICIO AL PARTICIPAR EN ESTE ESTUDIO DE INVESTIGACIÓN?

Usted no se beneficiará al participar en este estudio de investigación. Sin embargo, puede haber un beneficio general para la sociedad al fomentar el conocimiento científico. La información que se obtenga del uso de sus tejidos nos ayudará a entender mejor la enfermedad pulmonar y nos ayudará a establecer las estrategias de detección molecular para la detección temprana de la enfermedad pulmonar y el cáncer de pulmón.

¿QUÉ OTRAS OPCIONES TENGO SI NO PARTICIPO EN ESTE ESTUDIO DE INVESTIGACIÓN?

Usted puede elegir no participar en este estudio.

¿ME PAGARÁN POR PARTICIPAR EN EL ESTUDIO?

Si decide participar en este estudio de investigación, le recompensaremos (daremos) por su tiempo y sus gastos (\$5.00 por cada una de las 6 pruebas de laboratorio tal como se resume en la sección de procedimientos y \$45 por el procedimiento de la broncoscopia por una cantidad máxima de \$75.00).

Si no completa el estudio, su pago será de manera proporcional (pago modificado).

Le pediremos su número de seguro social para poder procesar su pago.

¿QUIÉNES PUEDEN VER MIS REGISTROS?

- Los registros de la investigación se mantendrán confidenciales y su nombre no se usará en ningún informe escrito o verbal.
- Sus registros de la investigación y sus expedientes médicos pueden ser examinados por los miembros del equipo de investigación y otras instituciones que participan en este estudio. Estas instituciones son: la Administración de Alimentos y Medicamentos de los Estados Unidos (*U.S. Food and Drug Administration, FDA*), los Institutos Nacionales de la Salud (*National Institutes of Health, NIH*), las oficinas del Departamento de Salud y Servicios Humanos (*Department of Health and Human Services, DHHS*), las agencias gubernamentales en otros países, las agencias federales involucradas en la investigación, las agencias gubernamentales a las que se deben informar ciertas enfermedades (enfermedades de declaración obligatoria).

- El investigador y el personal de la investigación examinarán sus expedientes médicos y mantendrán la información confidencial.
- Los registros de la investigación se guardarán de manera segura y los registros computarizados se protegerán con una contraseña.
- Las personas que examinaron este estudio de investigación como miembros del Comité de Investigaciones Clínicas (*Committee on Clinical Investigations, CCI*) de la Escuela de Medicina Albert Einstein y de la Junta de Revisión Institucional (*Institutional Review Board, IRB*) del Centro Médico Montefiore también pueden examinar sus registros de la investigación y sus expedientes médicos.
- La Oficina para la Protección de los Seres Humanos en la Investigación (*Office for Human Research Protections, OHRP*) también puede examinar sus registros del estudio de investigación.
- Los registros de la investigación se guardarán de manera segura y los registros computarizados se protegerán con una contraseña en el Centro de Investigaciones Clínicas (*Clinical Research Center, CRC*) de la Escuela de Medicina Albert Einstein.
- El personal del Centro de Investigaciones Clínicas, así como el personal de la investigación autorizado por el investigador tendrán acceso a estos registros.
- A todos estos grupos se les ha pedido mantener su nombre de manera confidencial.

¿QUÉ PASA SI ME LESIONO PORQUE PARTICIPÉ EN ESTE ESTUDIO DE INVESTIGACIÓN?

Si tiene alguna lesión física como resultado de esta investigación, el hospital participante solamente le proveerá tratamiento médico inmediato, esencial, y a corto plazo para la lesión, libre de costo para usted.

- No se le ofrecerá ninguna compensación monetaria.
- Usted no renuncia a ninguno de sus derechos legales al firmar este consentimiento informado.
- Si se requiere tratamiento adicional como resultado de una lesión física relacionada con la investigación, se le proveerá tratamiento médico necesario y la factura se enviará a su compañía de seguro o a usted como parte de sus gastos médicos.

Informe de inmediato cualquier molestia, dolencia o lesión que presente durante el curso de su participación en el estudio al Dr. Simon Spivack llamando al número 718-678-1040 de 9 a.m. a 5 p.m.

¿HABRÁ ALGÚN COSTO PARA MÍ?

No habrá ningún costo para usted por participar en este estudio.

¿SE ME PUEDE PEDIR QUE DEJE DE PARTICIPAR EN ESTE ESTUDIO ANTES DE QUE EL ESTUDIO TERMINE?

Si se alcanza la meta del estudio, podemos pedirle que deje de participar en este estudio.

¿QUIÉN PUEDE RESPONDER A MIS PREGUNTAS SOBRE EL ESTUDIO?

Nombre del investigador: Dr. Simon Spivack

Dirección de oficina: 1301 Morris Park Avenue, Price Center 268 Bronx, NY 10467

Número de teléfono: 718-678-1040

- Si tiene alguna pregunta relacionada con este proyecto de investigación, o cree que tiene alguna lesión relacionada con este estudio, puede llamar al investigador que se nombra arriba.
- Si tiene alguna pregunta sobre sus derechos como participante de la investigación, también puede llamar al jefe del Comité de Investigaciones Clínicas de la Escuela de Medicina Albert Einstein al número telefónico (718) 430-2253, de lunes a viernes de 9 a.m. a 5 p.m.

¿SE USARÁ ALGUNA DE LAS MUESTRAS (SANGRE, TEJIDO, ADN) QUE SE ME TOMARON PARA ESTUDIOS DE INVESTIGACIÓN FUTUROS?

USO DE MUESTRAS NO IDENTIFICADAS PARA INVESTIGACIONES FUTURAS:

Además de la investigación a la que usted ha decidido participar por medio de este estudio de investigación, el Dr. Simon Spivack u otros investigadores en esta institución u otras instituciones puede(n) querer estudiar las muestras en investigaciones futuras, entre ellas análisis genéticos. Estas muestras, que se tomaron de su cuerpo, NO serán relacionadas con usted. Nadie sabrá su nombre ni su información médica protegida.

En este momento, el investigador no sabe cuáles serán los estudios futuros. Sus muestras también se pueden enviar a un banco de tejido/células/ADN. Las muestras se pueden guardar durante mucho tiempo y pueden exceder los 50 años.

En algunas investigaciones en las que se utilizan sangre o tejido humano, las muestras y las partes de estas muestras pueden permitir a los investigadores desarrollar pruebas médicas o tratamientos médicos que tengan valor comercial. Usted no recibirá ningún dinero que pueda resultar de alguna de tales pruebas comerciales o tratamientos.

Sus muestras se pueden usar para investigaciones futuras a pesar de que el propósito de la investigación futura no se conoce en este momento

PARTICIPANTE:

POR FAVOR INDIQUE SU ELECCIÓN ESCRIBIENDO SUS INICIALES (PRIMERA LETRA DE SU NOMBRE Y APELLIDO) EN UNA (1) DE LAS SIGUIENTES OPCIONES

_____ Doy mi consentimiento para que mis muestras se utilicen en estudios de investigación futuros.

_____ Doy mi consentimiento para que mis muestras se utilicen en estudios de investigación futuros solamente para el estudio de _____.

_____ NO doy mi consentimiento para que mis muestras se utilicen en estudios de investigación futuros. (Las muestras serán destruidas al final del estudio).

¿QUÉ SUCEDERÁ SI INFORMACIÓN NUEVA SE HACE DISPONIBLE?

Si el doctor del estudio de investigación obtiene información nueva que pueda hacerle cambiar de opinión sobre continuar en este estudio, el doctor del estudio de investigación se lo informará.

Si usted decide retirarse del estudio, el doctor del estudio de investigación y su doctor personal harán arreglos para que su atención médica continúe.

¿PUEDO DEJAR DE PARTICIPAR EN EL ESTUDIO EN CUALQUIER MOMENTO?

- Su participación en este estudio es voluntaria, y puede dejar de participar en el estudio en cualquier momento sin tener que dar ninguna explicación.
- Si decide participar en el estudio y lo abandona después, parte de su información puede que ya se haya ingresado al estudio y eso no se podrá eliminar.
- Además, a usted se le puede pedir que regrese a ver al doctor del estudio de investigación nuevamente para hacer cualquier prueba final, y así cerrar el registro y las pruebas o el monitoreo que son necesarios para su salud como resultado de su participación. Estos resultados se pueden registrar.
- El tratamiento que recibe por parte de los doctores y del personal en la institución o las instituciones involucrada(s) en este estudio, no será afectado de ningún modo, ni ahora ni en el futuro, si usted acepta participar en este estudio y después lo abandona.

¿CUÁLES SON MIS DERECHOS SI PARTICIPO EN ESTE ESTUDIO DE INVESTIGACIÓN?

- Su participación en este estudio es voluntaria.
- Usted no renuncia a ninguno de sus derechos legales al participar en este estudio de investigación.
- El tratamiento que usted recibe por parte de los doctores y del personal en la institución o las instituciones involucrada(s) en este estudio, no será afectado de ningún modo, ni ahora ni en el futuro, si usted se niega a participar en este estudio o si ingresa al estudio y después lo abandona.

CERTIFICADO DE CONFIDENCIALIDAD

Con el fin de proteger su privacidad, hemos obtenido un certificado de confidencialidad de los Institutos Nacionales de la Salud de los Estados Unidos (*National Institutes of Health*), que es la que financia este estudio. Si la información de este estudio fuera solicitada u ordenada por una orden judicial por las agencias del gobierno o las cortes, usaremos este certificado para legalmente negarnos a proporcionar tal información. Esto es una situación poco probable - solamente en unas pocas ocasiones, los investigadores tuvieron que usar el certificado, y se respetó la mayor parte del tiempo, pero no siempre. Existen varios tipos de situaciones en las que el certificado no es aplicable. Sin embargo, se nos exige, por ejemplo, denunciar abuso infantil y algunas enfermedades, y debemos poner a disposición del gobierno la información para un análisis o una evaluación de nuestra investigación. El certificado de confidencialidad no le impide a usted o a un familiar suyo compartir información de manera voluntaria. De manera similar, si una compañía de seguros, empleador u otra persona obtiene su autorización por escrito para recibir información sobre la investigación, entonces los investigadores no pueden usar el certificado de confidencialidad para no entregar esa información.

Página de firmas para la obtención del consentimiento informado

Lo siguiente es una lista de los temas del estudio de investigación sobre los cuales hemos hablado. Si usted tiene alguna pregunta sobre alguno de estos temas, por favor pídale a la persona con la que está hablando sobre el estudio que le dé más información antes de aceptar participar en el estudio.

- De qué trata el estudio.
- Qué debo hacer cuando esté en el estudio.
- Los posibles riesgos y beneficios para mí.
- A quién contactar si tengo preguntas o si hay alguna lesión relacionada con el estudio.
- Información sobre costos y pagos.
- Puedo dejar de participar en el estudio en cualquier momento sin recibir ninguna sanción.
- Información sobre otras opciones.
- Toda información escrita y publicada se informará como datos grupales y no se hará mención a mi nombre.
- Me han dado el nombre del investigador y de otros para contactarlos.
- Tengo el derecho de preguntar cualquier duda.

Nombre en letra de imprenta del
participante

Firma del participante

Fecha

Nombre en letra de imprenta de la
persona que lleva a cabo el proceso
del consentimiento informado

Firma de la persona que lleva a
cabo el proceso del consentimiento
informado

Fecha

Nombre del intérprete

Firma del intérprete

Fecha

**ALBERT EINSTEIN COLLEGE OF MEDICINE OF YESHIVA UNIVERSITY
MONTEFIORE MEDICAL CENTER**

**INDIVIDUAL INFORMATION AND CONSENT FORM
Group 3 Controls Consent Form**

You are being asked to join this research study.

The title of the study is: Genetics of Lung Disease (Exhaled Breath Markers in Lung Carcinogenesis)

The study is being done under the supervision of:

Principal Investigator (Researcher Study Doctor): Simon Spivack M.D.

Office Address: Price Center 268 1301 Morris Park Avenue, Bronx, NY10467

Telephone#: 718 678-1040

Protocol #: 2007-407-000

Disclosure: The PI, Dr. Simon Spivack, has received a patent on a specific way of testing for DNA methylation (changes) called GC-tagged Bisulfite Genomic Sequencing. This method is being used in the current study. Based on data from this and other research, the potential financial value of this testing method may be increased. Thus, the Institution and the PI have a potential financial interest in the outcome of this study.

DO I HAVE TO TAKE PART IN THIS RESEARCH STUDY?

- Your participation is voluntary. This means that you decide whether or not you want to join the study after speaking with the researcher, or other member of the research team.
- If you decide to take part you will be asked to sign this consent form. Your signature means that you agree to be a subject in this research.
- After reading this form and having a discussion about what it says, you should ask all the questions you want to ask. You should take as much time as you need to make a decision.
- If you do not understand some of the terms used in this form, ask the person who is discussing the study with you to give any additional information that may make this easier to understand.
- You do not have to consent to participate in the study immediately, or ever. Take time to decide whether or not you wish to join. You may take home a copy of this consent form to think about it or discuss the information with family or friends before you decide.
- If you decide not to participate, the care providers at this facility will give you all of the standard care that is appropriate for you.
- You will be given a copy of this form whether or not you agree to participate in this study. Do not sign the form unless you have had all your questions answered and understand exactly what is involved.
- If you decide to take part you are still free to withdraw at any time without giving a reason. This will not affect your care and you will continue to be treated at this facility.
- The form discusses:

- What the researchers will learn from the research
- What will happen to you during the research
- What risks and/or discomforts you might expect/experience as a research subject
- If you can expect any benefits, and are there any alternatives to this research for your condition.

WHY HAVE I BEEN ASKED TO TAKE PART IN THIS RESEARCH STUDY?

- Because you have no known current diagnosis of lung cancer, and/or are being re-CT scanned for screening for lung cancer.
- To serve as a comparison (control group) to establish biological and statistical significance.

WHY IS THIS RESEARCH STUDY BEING DONE?

- This research will attempt to establish a relationship between the molecular changes that occur in cells from the mouth, saliva, sputum, exhaled breath and blood as they relate to the development of lung disease. If this relationship can be proven, it maybe possible in the future to test for certain lung diseases with a simple laboratory test.
- Dr. Simon Spivack, the principal investigator, is conducting a research investigation to determine whether the activity of certain genes and proteins in the lung and other tissues increases with exposure to cigarette smoke or environmental hazards. This increased activity might impact the development of lung disease. Genes instruct proteins to control and direct many activities of cells in the human body. The genes of interest to this investigation include inhaled foreign compound-processing genes, certain cancer-associated genes, and other genes, proteins and biological markers associated with the metabolism of foreign substances, cellular processes, and other lung disease related processes. The activity of genes and proteins found in the lung are thought to parallel that detected in blood, saliva, sputum, exhaled breath condensate (moisture) and mouth cells. This is unproven. Additionally, the relationship of these genes' activity to lung diseases, including lung cancer, remains unproven.

HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

You will be one of approximately 2000 who will be participating in this study at Montefiore Medical Center and Albert Einstein College of Medicine.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

We expect that you will be in this research study from the time informed consent is signed until you complete the interview process and specimen collection (40 minutes).

PROCEDURES:

- You will be asked to complete a questionnaire regarding the amount you have smoked, your diet, other environmental exposures, medication and family history. This

information is crucial to this study. The questionnaire will be administered by research nurses study staff and takes about 15 minutes to complete.

- There are six (6) specimens study staff would like to collect:
 - Extra tubes of blood (30 mls or about 2 tablespoons of (blood) if possible will be drawn at the same time as your blood tests to avoid extra needle sticks.
 - A collection of mouth cells by rinsing your mouth with an over-the-counter mouthwash solution.
 - A manually spinning soft brush will be held against the lining of each cheeks four times to collect additional mouth cells.
 - A collection of your exhaled breath condensate (EBC) will be collected. This will be done by having you rinse your mouth with water and then breathing normally into a disposable portable mouthpiece for 10-15minutes to collect 1 ml (less than one quarter teaspoon) of EBC. We may ask you to repeat this process up to 4-5 times at this session. Although it is your option to choose to limit this number of EBC collections to one or any other number. It maybe necessary to wear a nose clip during the collection.
 - A collection of your saliva will be obtained by spitting directly into a cup. A second collection of your saliva will be obtained by chewing on a cotton-wool swab called a salivette for about 30 to 60 seconds. One can measure cotinine, reflective on smoking, in the saliva, in addition to other measurements.
 - A collection of your sputum will by collected by taking a deep breath and coughing sputum (phlegm) directly into a collection cup. If you are unable to collect sputum this way we may give you a saline nebulizer for 10 minutes to moisten the airway and than ask you to take a deep breath and cough sputum directly into a collection cup.
- Specimens are collected by research staff or phlebotomy staff. Specimen collection takes about 20-30 minutes.
- RISK: There is no additional risk in participation in this study.

ADDITIONAL TESTS ON YOUR SAMPLE:

- In the future because of the acquisition of new knowledge through research and advances in techniques in the field of genetic testing, the investigator may wish to conduct other biologic and genetic testing focused solely on the susceptibility to lung cancer and other lung diseases caused by inhaled toxins, or other substances. This gives consent for possible further testing on your specimens. The additional tests would be focused on foreign compound-processing genes ,cancer-associated genes and other genes, proteins and biologic markers associated with the metabolism of foreign substances, cellular function, and other lung disease-relevant phenomena. All previously mentioned assurances for your confidentiality will be maintained. The results of all genetic testing will not be made available to you. If you would like to speak with a genetics counselor about general information concerning the storage of genetic specimens, you may call one.
- Since the significance of these tests are not known for you, we will not disclose the results of the genetic testing. No formal counseling will be provided under the research study. If your equest,you will be referred to a genetic counselor. You or your insurance carrier will be responsible for the genetic counselor's fee.

WILL THIS STUDY INVOLVE GENETIC RESEARCH and/or TESTING

This research study is designed to explore the genes and molecules that maybe responsible for the susceptibility and/or development of lung disease in anticipation of establishing molecular screening strategies for the early detection of lung diseases, including cancer.

- Tests conducted under this research study may reveal genetic information.
- **GENETIC COUNSELING INFORMATION:** You may wish to obtain professional genetic counseling prior to signing the informed consent. A genetic counselor is a person qualified to provide information about what the results of this type of test may mean to you and your family. You or your insurance company will be responsible for the cost of these services.

WHAT ARE THE POSSIBLE SIDE EFFECTS, DISCOMFORTS, RISKS OR INCONVENIENCES I CAN EXPECT FROM BEING IN THIS RESEARCH STUDY?

Here is a list of the known risks associated with this research:

- **Questionnaire:** Occasionally, the discussion about smoking history or environmental contaminant exposure during the interview process may provoke anxiety.
- **Blood:** Rarely, is an extra needle stick required to collect the blood specimens. The risks involved in blood sampling are infection (rare) and bruising and pain (occasionally).
- **Mouth:** swabs with soft brushes rarely may cause discomfort and bleeding. The mouthwash solution causes a tingling sensation that resolves quickly and rarely is a cause for discomfort.
- **Exhaled breath condensate:** collection is anon-invasive test and does not have any known risk. You may feel uncomfortable from breathing into a tube and possibly wearing a nose clip for 10-15 minutes.
- **Saliva:** collection does not have any known risk.
- **Sputum:** The risk regarding the sputum induction include cough, falling oxygen level in the blood, and bronchospasm especially in asthmatics.

WILL THE RESULTS OF THIS STUDY OR ANY OF THE PROCEDURES AFFECT MY INSURABILITY?

The tests done under this study will not affect your ability to get or keep medical, health or life insurance.

ARE THERE LIKELY TO BE ANY BENEFITS TO TAKING PART IN THIS RESEARCH STUDY?

You will not benefit from being in this research study. However, there may be a general benefit to society by the furthering of scientific knowledge. The information gained by using your tissues will help us better understand lung disease and help us establish molecular screening strategies for the early detection of lung disease and lung cancer.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS RESEARCH STUDY?

You may choose not to participate in this study.

WILL I BE PAID FOR BEING IN THE STUDY?

If you agree to take part in this research study, we will compensate (give) you for your time and expenses (\$5.00 each for 6 lab tests as outlined in procedures section for maximum amount of (\$30.00).

If you do not complete the study, your payment will be prorated. We will be collecting your social security number in order to process your payment.

WHO MAY SEE MY RECORDS?

- The research records will be kept private and your name will not be used in any written or verbal reports.
- Your research records and medical records maybe inspected by members of the research team and other institutions that participate in this study. These are: The U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), Department of Health and Human Services (DHHS) offices, New York State Department of Health (NYSDOH), Governmental agencies in other countries, Federal agencies involved with research, governmental agencies to whom certain diseases (reportable diseases) must be reported.
- The researcher and research staff will review your medical records and will keep the information private.
- The research records will be kept in a secured manner and computer records will be password protected.
- The people who reviewed this research study as members of the Albert Einstein College of Medicine Committee on Clinical Investigations (CCI) and the Montefiore Medical Center Institutional Review Board (IRB) may also review your research and medical records.
- The Office of Human Research Protections (OHRP) may also review your research study records.
- The research records will be kept in a secured manner and computer records will be password protected in the Albert Einstein College of Medicine Clinical Research Center (CRC).
- The Clinical Research Center staff, as well as the research personnel authorized by the researcher will have access to these records.
- All of these groups have been requested to keep your name private.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

If there is a physical injury as a result of this research, only immediate, essential, short-term medical treatment as determined by the participating hospital, will be available for the injury without charge to you personally.

- No monetary compensation will be offered.

- You are not waiving any of your legal rights by signing this informed consent document
- If additional treatment is required as a result of a physical injury related to the research, necessary medical treatment will be provided to you and billed to your insurance company or to you as part of your medical expenses.

Immediately report any discomforts, problems or injuries you experience during the course of your participation in the study to Dr. Simon Spivack at 718 678-1040 between the hours of 9am to 5pm.

WILL THERE BE ANY COSTS TO ME?

There will be no costs to you for participating in this study.

CAN I BE ASKED TO STOP PARTICIPATING IN THIS STUDY BEFORE THE STUDY IS FINISHED?

If the study goal has been reached, you can be asked to stop participating.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

Researcher's Name: Dr. Simon Spivack

Office Address: 1301 Morris Park Avenue PriceCenter268Bronx, NY10467

Office Phone: 718-678-1040

- If any questions arise related to this research project, or you believe you have any injury related to this study, you can call the researcher above.
- If you have questions regarding your rights as a research subject, you may also call the Manager of The Albert Einstein College of Medicine Committee on Clinical Investigations at (718)430-2253, Monday through Friday between 9AM and 5 PM.

WILL ANY OF THE SAMPLES (BLOOD, TISSUE, DNA) TAKEN FROM ME BE USED FOR FUTURE RESEARCH STUDIES?

USE OF DE-IDENTIFIED SPECIMENS FOR FUTURE RESEARCH:

In addition to the research you are consenting to under this research study, **Dr. Simon Spivack** or other researchers at this or other institutions, and federal agencies such as NIH, may wish to study the samples in future research, including genetic analysis. These samples, taken from your body, would NOT be linked back to you. No one will know your name or protected health information. Therefore, no additional risk to privacy is expected from this sharing. All names and other identifiers are under double lock and password, and held by the research coordinator, not the scientist.

At this time, the researcher does not know what the future studies will be. Your specimens and data may also be submitted to a tissue/cell/DNA bank. The specimens may be kept for a long time and may exceed 50 years.

In some research using human blood or tissue, the specimens and their parts may enable researchers to develop medical tests or treatments that have commercial value. You will not receive any money that may result from any such commercial tests or treatments.

Your specimens and data maybe used for future research, even though the purpose of the future research is not known at this time.

PARTICIPANT:

PLEASE INDICATE YOUR CHOICE BY INITIALING ONE (1) OF THE FOLLOWING OPTIONS

___ I consent to have my specimens used for future research studies.

___ I consent to have my specimens used for future research studies only for the study of.

___ I do NOT consent to have my specimens used for future research studies. (The specimens will be destroyed at the end of the study.)

WHAT IF NEW INFORMATION BECOMES AVAILABLE?

- If the research study doctor obtains new information that might lead you to change your mind about continuing in this study, the research study doctor will tell you about it.
- If you decide to withdraw, the research study doctor and your personal doctor will make arrangements for your care to continue.

MAY I STOP THE STUDY AT ANY TIME?

- Your participation in this study is voluntary, and you may withdraw from the study at any time without giving a reason.
- If you agree to participate and withdraw at a later time, some of your information may have already been entered into the study and that will not be removed.
- In addition, you may be asked to return to the research study doctor again for any final tests in order to close the record and tests or monitoring that are necessary for your health as a result of your participation. These results maybe recorded.
- Your treatment by doctors and staff at the institution(s)involved in this study, now and in the future, will not be affected in any way if you agree to participate and withdraw later.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS RESEARCH STUDY?

- Your participation in this study is voluntary.
- You do not waive any of your legal rights by participating in this research study.

Your treatment by doctors and staff at the institution(s)involved in this study, now and in the future, will not be affected in anyway if you refuse to participate or if you enter the study and withdraw later.

CERTIFICATE OF CONFIDENTIALITY

As a way to protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health, which is funding this study. If information from this study was requested or subpoenaed by government agencies or the courts, we will use the Certificate to attempt to legally refuse to provide it. This is rare – in only a few cases did researchers have to use the Certificate, and it was honored most of the time, but not every time. There are several kinds of situations that the Certificate does not apply. For example, we are still required to report child abuse and some diseases, and we must make data available to the government for a review or evaluation of our research. The Certificate does not prevent you or a member of your family from voluntarily sharing information. Similarly, if an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

INFORMED CONSENT SIGNATURE PAGE

The following is a list of items we discussed about this research study. If you have any questions about any of these items, please ask the person who is discussing the study with you for more information before agreeing to participate.

- What the study is about.
- What I must do when I am in the study.
- The possible risks and benefits to me.
- Who to contact if I have questions or if there is a research related injury.
- Any costs and payments.
- I can discontinue participating in the study at anytime without penalty.
- Other choices.
- All written and published information will be reported as group data with no reference to my name.
- I have been given the name of the researcher and others to contact.
- I have the right to ask any questions.

Printed Name of Participant

Signature of Participant

Date

Printed Name of Person Conducting the
Informed Consent Process

Signature of Person Conducting the
Informed Consent Process

Date

Formulario de consentimiento para los grupos de control, Grupo 3

ALBERT EINSTEIN COLLEGE OF MEDICINE OF YESHIVA UNIVERSITY MONTEFIORE MEDICAL CENTER

Información para el participante y formulario de consentimiento

Se le está pidiendo que participe en este estudio de investigación.

El nombre del estudio es: Genética de la enfermedad pulmonar (marcadores en aire exhalado en la carcinogénesis pulmonar)

El estudio se está llevando a cabo bajo la supervisión de:

Investigador principal (doctor del estudio de investigación): Simon Spivack, MD

Dirección de oficina: 1301 Morris Park Avenue, Price Center Room 268

Bronx, NY 10467

Número de teléfono: 718-678-1040

Número de protocolo: 2007-407-000

Declaración: El investigador principal, Dr. Simon Spivack, ha recibido una patente de una forma específica de analizar la metilación (cambios) del ADN que se llama GC (guanina y citosina) etiquetada con la secuenciación genómica de bisulfito. Este método se está usando en el estudio actual. En base a los datos de ésta y otras investigaciones, puede ser que el posible valor económico de este método de prueba aumente. De esta manera, la institución y el investigador principal tienen un posible interés económico en el resultado de este estudio.

¿TENGO QUE PARTICIPAR EN ESTE ESTUDIO DE INVESTIGACIÓN?

- Su participación es voluntaria. Esto quiere decir que usted decide si quiere participar el estudio o no después de hablar con el investigador, u otro miembro del equipo de investigación.
- Si decide participar en el estudio, le pediremos que firme este formulario de consentimiento. Su firma significa que usted acepta ser participante en esta investigación.
- Después de que usted lea este formulario y haya hablado sobre lo que trata el formulario, usted debe preguntar todo lo que quiere saber. Debe tomarse el tiempo que necesite antes de tomar una decisión.
- Si no entiende algunas de las palabras que se usan en este formulario, pídale a la persona con la que usted está hablando sobre el estudio que le dé información adicional que le permita entender más fácilmente.
- Usted no tiene que aceptar participar en el estudio ahora o en el futuro. Tómese su tiempo para decidir si desea participar o no. Usted puede llevarse una copia de este formulario de consentimiento para que lo piense o pueda comentar la información a su familia o sus amistades antes de tomar una decisión.
- Si usted decide no participar, los proveedores de atención médica en este centro le brindarán toda la atención médica habitual apropiada para usted.

- A usted se le dará una copia de este formulario, ya sea si acepta participar o no en este estudio. No firme el formulario a menos que le hayamos respondido a todas sus preguntas y entienda exactamente de lo que trata el estudio.
- Si decide participar en el estudio, todavía tiene la libertad de retirarse del estudio en cualquier momento sin tener que dar ninguna explicación. El retirarse del estudio no afectará su atención médica y usted continuará su tratamiento en este centro.
- El formulario trata sobre:
 - LO QUE LOS INVESTIGADORES SABRÁN DE LA INVESTIGACIÓN. LO QUE LE PASARÁ A USTED DURANTE LA INVESTIGACIÓN.
 - LOS RIESGOS Y/O LAS MOLESTIAS QUE PUEDE ESPERAR/PRESENTAR COMO PARTICIPANTE DE LA INVESTIGACIÓN.
 - SI USTED PUEDE RECIBIR ALGÚN BENEFICIO, Y SI ¿HAY ALGUNA ALTERNATIVA A ESTA INVESTIGACIÓN PARA SU ENFERMEDAD?

¿POR QUÉ ME HAN PEDIDO QUE PARTICIPE EN ESTE ESTUDIO DE INVESTIGACIÓN?

Le estamos pidiendo que participe en el estudio de investigación:

- Porque no tiene un diagnóstico de cáncer de pulmón en la actualidad, y/o se le está volviendo a hacer una tomografía computarizada para la detección del cáncer de pulmón.
- Para servir como comparación (grupo de control), y así establecer la importancia biológica y estadística.

¿POR QUÉ SE ESTÁ HACIENDO ESTE ESTUDIO DE INVESTIGACIÓN?

- Esta investigación tratará de establecer la relación entre los cambios moleculares que ocurren en las células de la boca, la saliva, el esputo, el aire exhalado y la sangre en relación al desarrollo de la enfermedad pulmonar. Si esta relación se puede probar, puede ser posible que en el futuro se hagan pruebas para detectar ciertas enfermedades pulmonares con una prueba de laboratorio más simple.
- El Dr. Simon Spivack, el investigador principal, es el que está llevando a cabo la investigación para determinar si la actividad de ciertos genes y proteínas en el pulmón y en otros tejidos aumenta con la exposición al humo del cigarrillo o a los peligros ambientales. El incremento de esta actividad puede tener un efecto en el desarrollo de la enfermedad pulmonar. Los genes ordenan a las proteínas a controlar y dirigir muchas actividades de las células en el cuerpo humano. Los genes que son de interés para esta investigación incluyen los genes de procesamiento de compuestos extraños inhalados, ciertos genes relacionados con el cáncer y otros genes, marcadores proteínicos y biológicos relacionados con el metabolismo de sustancias extrañas, procesos celulares u otros procesos relacionados con la enfermedad pulmonar. Se cree que la actividad de los genes y las proteínas encontradas en los pulmones son iguales a aquella detectada en la sangre, la saliva, el esputo, el condensado de aire exhalado (humedad) y las células de la boca. Esto no está probado. Además, la relación de la actividad de estos genes con las enfermedades pulmonares, incluyendo el cáncer de pulmón, continúa sin probarse.

¿CUÁNTAS PERSONAS PARTICIPARÁN EN ESTE ESTUDIO DE INVESTIGACIÓN?

Usted será una(o) de aproximadamente 2 000 personas que estarán participando en este estudio en el Centro Médico Montefiore (*Montefiore Medical Center*) y en la Escuela de Medicina Albert Einstein (*Albert Einstein College of Medicine*).

¿QUÉ SUCEDERÁ SI PARTICIPO EN ESTE ESTUDIO DE INVESTIGACIÓN?

Esperamos que participe en este estudio de investigación desde el momento que usted firme el consentimiento informado hasta que complete el proceso de la entrevista y la recolección de muestras (40 minutos).

PROCEDIMIENTOS:

- Le pediremos que complete un cuestionario sobre la cantidad de cigarrillos que ha fumado, los alimentos que come, otras exposiciones ambientales, medicamentos, y antecedentes familiares. Esta información es de suma importancia para este estudio. Un(a) enfermero(a) de investigación del personal del estudio le tomará el cuestionario y durará cerca de 15 minutos completarlo.
- El personal del estudio recolectará seis (6) muestras:
 - Se le extraerán tubitos adicionales de sangre (30 mililitros o unas 2 cucharadas de sangre) si fuera posible al mismo tiempo que se le hagan sus pruebas de sangre para evitar pinchazos de agujas adicionales.
 - Se recolectarán células de la boca enjuagándose la boca con una solución de enjuague bucal que es sin receta médica.
 - Se recolectarán células de la boca adicionales sosteniendo cuatro veces un cepillo suave de uso manual contra el revestimiento de cada mejilla.
 - Se recolectará una muestra de condensado de aire exhalado (CAE). Esta muestra se le tomará por medio del enjuague de la boca con agua y luego respirará normalmente en una boquilla portátil descartable de 10 a 15 minutos para recolectar 1 mililitro (menos de un cuarto de cucharadita) de condensado de aire exhalado. Es posible que le pidamos que repita este proceso hasta 4 a 5 veces en esta sesión. Aunque es su opción limitar las veces de esta recolección de condensado de aire exhalado a una vez o cualquier otro número de veces. Pueda que sea necesario usar una pinza nasal durante la recolección de la muestra.
 - Se recolectará una muestra de su saliva, tendrá que escupir en un vasito. Se recolectará una segunda muestra de su saliva la cual se obtendrá masticando un hisopo de algodón que se llama salivette de 30 a 60 segundos. Uno puede medir la cotinina, que se refleja al fumar, en la saliva, aparte de otras medidas.
 - Se recolectará una muestra de esputo (flema de la garganta). Respirará profundamente y toserá el esputo directamente en el vaso para la muestra. Si usted no puede recolectar el esputo de esta manera, podemos darle un nebulizador salino por 10 minutos para humedecer las vías respiratorias y luego le pediremos que respire profundamente y tosa el esputo directamente en el vaso para la muestra.
- El personal de la investigación o el personal de flebotomía recolectarán las seis muestras. La recolección de las muestras dura de unos 20 a 30 minutos.
- RIESGO: No hay riesgos adicionales al participar en este estudio.

PRUEBAS ADICIONALES A SUS MUESTRAS:

- En el futuro debido al descubrimiento de nuevos conocimientos a través de investigaciones y avances en técnicas en el campo del análisis genético, el investigador puede hacer otros

análisis biológicos y genéticos enfocados solamente en la susceptibilidad al cáncer de pulmón y a otras enfermedades pulmonares causadas por las toxinas exhaladas u otras sustancias. Esto da consentimiento para realizar posibles análisis posteriores a sus muestras. Los análisis adicionales se enfocarán en los genes de procesamiento de compuestos extraños, genes relacionados con el cáncer y otros genes, marcadores proteínicos y biológicos relacionados con el metabolismo de sustancias extrañas, función celular y otros fenómenos relevantes a la enfermedad pulmonar. Se mantendrán todas las garantías mencionadas anteriormente para su confidencialidad. No estarán disponibles para usted los resultados de todos los análisis genéticos. Si usted desea hablar con un consejero genético sobre información general relacionada al almacenamiento de las muestras genéticas, puede llamar a un consejero genético.

- Como usted no sabe el efecto de estos análisis, nosotros no revelaremos los resultados de los análisis genéticos. No se ofrecerá consejería oficial para este estudio de investigación. Si usted pide consejería, se le referirá a un consejero genético. Usted o su compañía de seguro médico serán responsables de los costos del consejero genético.

¿INVOLUCRARÁ ESTE ESTUDIO INVESTIGACIÓN GENÉTICA y/o ANÁLISIS GENÉTICOS?

Este estudio de investigación está diseñado para la exploración de genes y moléculas que pueden ser responsables de la susceptibilidad y/o desarrollo de la enfermedad pulmonar anticipándose al establecimiento de las estrategias de detección molecular para la detección temprana de las enfermedades pulmonares, incluyendo el cáncer.

- Las pruebas que se realicen para este estudio de investigación pueden revelar información genética.
- INFORMACIÓN SOBRE CONSEJERÍA GENÉTICA:** Usted puede querer consejería genética antes de firmar el consentimiento informado. Un consejero genético es una persona calificada para dar información sobre lo que pueden significar los resultados de este tipo de análisis para usted y su familia. Usted o su compañía de seguro serán responsables de los costos de estos servicios.

¿CUÁLES SON LOS POSIBLES EFECTOS SECUNDARIOS, MOLESTIAS, RIESGOS O INCONVENIENTES QUE PUEDO ESPERAR AL PARTICIPAR EN ESTE ESTUDIO DE INVESTIGACIÓN?

Aquí hay una lista de los riesgos conocidos relacionados con esta investigación:

- Cuestionario:** Algunas veces, el hablar sobre el historial del tabaquismo o la exposición a contaminantes ambientales durante la entrevista puede producirle ansiedad.
- Sangre:** Raras veces, se necesita un pinchazo adicional para recolectar muestras de sangre. Los riesgos involucrados en la obtención de la muestra de sangre son infección (poco frecuente), y moretón y dolor (a veces).
- Células de la boca:** Los hisopos con cepillos suaves raras veces causan molestias y sangrado. La solución de enjuague bucal causa una sensación de cosquilleo que desaparece rápidamente y en raras ocasiones causa molestia.
- Condensado de aire exhalado:** La recolección del condensado de aire exhalado es una prueba no invasiva y no tiene ningún riesgo conocido. Usted puede sentir incomodidad al respirar en un tubo y posiblemente usar una pinza nasal de 10 a 15 minutos.

- Saliva: La recolección de la saliva no tiene ningún riesgo conocido.
- Espujo: El riesgo relacionado con la provocación del espujo incluye tos, disminución del nivel de oxígeno en la sangre, y broncoespasmos (estrechez de las vías respiratorias) en especial en personas con asma.

¿AFECTARÁN LOS RESULTADOS DE ESTE ESTUDIO O CUALQUIERA DE LOS PROCEDIMIENTOS LA OBTENCIÓN DE SEGURO MÉDICO?

Las pruebas que se realizan para este estudio no afectarán su capacidad obtener o conservar su seguro médico, seguro de salud o seguro de vida.

¿ES POSIBLE QUE HAYA ALGÚN BENEFICIO AL PARTICIPAR EN ESTE ESTUDIO DE INVESTIGACIÓN?

Usted no se beneficiará al participar en este estudio de investigación. Sin embargo, puede haber un beneficio general para la sociedad al fomentar el conocimiento científico. La información que se obtenga del uso de sus tejidos nos ayudará a entender mejor la enfermedad pulmonar y nos ayudará a establecer las estrategias de detección molecular para la detección temprana de la enfermedad pulmonar y el cáncer de pulmón.

¿QUÉ OTRAS OPCIONES TENGO SI NO PARTICIPO EN ESTE ESTUDIO DE INVESTIGACIÓN?

- Usted puede elegir no participar en este estudio.

¿ME PAGARÁN POR PARTICIPAR EN EL ESTUDIO?

Si decide participar en este estudio de investigación, le recompensaremos (daremos) por su tiempo y sus gastos (\$5.00 por cada una de las 6 pruebas de laboratorio tal como se resume en la sección de procedimientos por una cantidad máxima de \$30.00).

Si no completa el estudio, su pago será de manera proporcional (pago relativo). Le pediremos su número de seguro social para poder procesar su pago.

¿QUIÉNES PUEDEN VER MIS REGISTROS?

- Los registros de la investigación se mantendrán confidenciales y su nombre no se usará en ningún informe escrito o verbal.
- Sus registros de la investigación y sus expedientes médicos pueden ser examinados por los miembros del equipo de investigación y otras instituciones que participan en este estudio. Estas instituciones son: la Administración de Alimentos y Medicamentos de los Estados Unidos (*U.S. Food and Drug Administration, FDA*), los Institutos Nacionales de la Salud (*National Institutes of Health, NIH*), las oficinas del Departamento de Salud y Servicios Humanos (*Department of Health and Human Services, DHHS*), el Departamento de Salud del Estado de Nueva York (*New York State Department of Health, NYSDOH*), las agencias gubernamentales en otros países, las agencias federales involucradas en la investigación, las agencias gubernamentales a las que se deben informar ciertas enfermedades (enfermedades de declaración obligatoria).

- El investigador y el personal de la investigación examinarán sus expedientes médicos y mantendrán la información confidencial. Los registros de la investigación se guardarán de manera segura y los registros computarizados se protegerán con una contraseña.
- Las personas que examinaron este estudio de investigación como miembros del Comité de Investigaciones Clínicas (*Committee on Clinical Investigations, CCI*) de la Escuela de Medicina Albert Einstein y de la Junta de Revisión Institucional (*Institutional Review Board, IRB*) del Centro Médico Montefiore también pueden examinar sus registros de la investigación y sus expedientes médicos.
- La Oficina para la Protección de los Seres Humanos en la Investigación (*Office for Human Research Protections, OHRP*) también puede examinar sus registros del estudio de investigación.
- Los registros de la investigación se guardarán de manera segura y los registros computarizados se protegerán con una contraseña en el Centro de Investigaciones Clínicas (*Clinical Research Center, CRC*) de la Escuela de Medicina Albert Einstein.
- El personal del Centro de Investigaciones Clínicas, así como el personal de la investigación autorizado por el investigador tendrán acceso a estos registros.
- A todos estos grupos se les ha pedido mantener su nombre de manera confidencial.

¿QUÉ PASA SI ME LESIONO PORQUE PARTICIPÉ EN ESTE ESTUDIO DE INVESTIGACIÓN?

Si tiene alguna lesión física como resultado de esta investigación, el hospital participante solamente le proveerá tratamiento médico inmediato, esencial, y a corto plazo para la lesión, libre de costo para usted.

- No se le ofrecerá ninguna compensación monetaria.
- Usted no renuncia a ninguno de sus derechos legales al firmar este consentimiento informado.
- Si se requiere tratamiento adicional como resultado de una lesión física relacionada con la investigación, se le proveerá tratamiento médico necesario y la factura se enviará a su compañía de seguro o a usted como parte de sus gastos médicos.

Informe de inmediato cualquier molestia, dolencia o lesión que presente durante el curso de su participación en el estudio al Dr. Simon Spivack llamando al número 718-678-1040 de 9 a.m. a 5 p.m.

¿HABRÁ ALGÚN COSTO PARA MÍ?

No habrá ningún costo para usted por participar en este estudio.

¿Se me puede pedir que deje de participar en este estudio antes de que el estudio termine?

Si se alcanza la meta del estudio, podemos pedirle que deje de participar en este estudio.

¿QUIÉN PUEDE RESPONDER A MIS PREGUNTAS SOBRE EL ESTUDIO?

Nombre del investigador: Dr. Simon Spivack

Dirección de oficina: 1301 Morris Park Avenue, Price Center 268 Bronx, NY 10467

Número de teléfono: 718-678-1040

- Si tiene alguna pregunta relacionada con este proyecto de investigación, o cree que tiene alguna lesión relacionada con este estudio, puede llamar al investigador que se nombra arriba.
- Si tiene alguna pregunta sobre sus derechos como participante de la investigación, también puede llamar al jefe del Comité de Investigaciones Clínicas de la Escuela de Medicina Albert Einstein al número telefónico (718) 430-2253, de lunes a viernes de 9 a.m. a 5 p.m.

¿SE USARÁ ALGUNA DE LAS MUESTRAS (SANGRE, TEJIDO, ADN) QUE SE ME TOMARON PARA ESTUDIOS DE INVESTIGACIÓN FUTUROS?

USO DE MUESTRAS NO IDENTIFICADAS PARA FUTURAS INVESTIGACIONES:

Además de la investigación a la que usted ha decidido participar por medio de este estudio de investigación, el Dr. Simon Spivack u otros investigadores en esta institución u otras instituciones, y agencias federales como el NIH, puede(n) querer estudiar las muestras en investigaciones futuras, entre ellas análisis genéticos. Estas muestras, que se tomaron de su cuerpo, durante esta cirugía médicamente necesaria que su médico ha recomendado **NO** serían relacionadas con usted. Nadie sabrá su nombre ni su información médica protegida. Por lo tanto, no se esperan riesgos adicionales de privacidad por compartir las muestras. Todos los nombres y otra información de identificación están bajo doble medida de seguridad y contraseña, y las cuales están solo en manos del coordinador de la investigación, y no de los científicos.

En este momento, el investigador no sabe cuáles serán los estudios futuros. Sus muestras también se pueden enviar a un banco de tejido/células/ADN. Las muestras se pueden guardar durante mucho tiempo y pueden exceder los 50 años.

En algunas investigaciones en las que se utilizan sangre o tejido humano, las muestras y las partes de estas muestras pueden permitir a los investigadores desarrollar pruebas médicas o tratamientos médicos que tengan valor comercial. Usted no recibirá ningún dinero que pueda resultar de alguna de tales pruebas comerciales o tratamientos.

Sus muestras y datos se pueden usar para investigaciones futuras a pesar de que el propósito de la investigación futura no se conoce en este momento.

PARTICIPANTE:

POR FAVOR INDIQUE SU ELECCIÓN ESCRIBIENDO SUS INICIALES (PRIMERA LETRA DE SU NOMBRE Y APELLIDO) EN UNA (1) DE LAS SIGUIENTES OPCIONES

_____ Doy mi consentimiento para que mis muestras se utilicen en estudios de investigación futuros.

_____ Doy mi consentimiento para que mis muestras se utilicen en estudios de investigación futuros solamente para el estudio de _____.

_____ NO doy mi consentimiento para que mis muestras se utilicen en estudios de investigación futuros. (Las muestras serán destruidas al final del estudio).

¿QUÉ SUCEDERÁ SI INFORMACIÓN NUEVA SE HACE DISPONIBLE?

Si el doctor del estudio de investigación obtiene información nueva que pueda hacerle cambiar de opinión sobre continuar en este estudio, el doctor del estudio de investigación se lo informará.

Si usted decide retirarse del estudio, el doctor del estudio de investigación y su doctor personal harán arreglos para que su atención médica continúe.

¿PUEDO DEJAR DE PARTICIPAR EN EL ESTUDIO EN CUALQUIER MOMENTO?

- Su participación en este estudio es voluntaria, y puede dejar de participar en el estudio en cualquier momento sin tener que dar ninguna explicación.
- Si acepta participar en el estudio y lo abandona después, parte de su información puede que ya se haya ingresado al estudio y eso no se podrá eliminar.
- Además, a usted se le puede pedir que regrese a ver al doctor del estudio de investigación nuevamente para hacer cualquier prueba final, y así cerrar el registro y las pruebas o el monitoreo que son necesarios para su salud como resultado de su participación. Estos resultados se pueden registrar.
- El tratamiento que recibe por parte de los doctores y del personal en la institución o las instituciones involucrada(s) en este estudio, no será afectado de ningún modo, ni ahora ni en el futuro, si usted acepta participar en este estudio y después lo abandona.

¿CUÁLES SON MIS DERECHOS SI PARTICIPO EN ESTE ESTUDIO DE INVESTIGACIÓN?

- Su participación en este estudio es voluntaria.
- Usted no renuncia a ninguno de sus derechos legales al participar en este estudio de investigación.
- El tratamiento que usted recibe por parte de los doctores y del personal en la institución o las instituciones involucrada(s) en este estudio, no será afectado de ningún modo, ni ahora ni en el futuro, si usted se niega a participar en este estudio o si ingresa al estudio y después lo abandona.

Certificado de confidencialidad

Con el fin de proteger su privacidad, hemos obtenido un certificado de confidencialidad de los Institutos Nacionales de la Salud de los Estados Unidos (*National Institutes of Health*), que es la que financia este estudio. Si la información de este estudio fuera solicitada u ordenada por una orden judicial por las agencias del gobierno o las cortes, usaremos este certificado para legalmente negarnos a proporcionar tal información. Esto es una situación poco probable - solamente en unas pocas ocasiones, los investigadores tuvieron que usar el certificado, y se respetó la mayor parte del tiempo, pero no siempre. Existen varios tipos de situaciones en las que el certificado no es aplicable. Sin embargo, se nos exige, por ejemplo, denunciar abuso infantil y algunas enfermedades, y debemos poner a disposición del gobierno la información para un análisis o una evaluación de nuestra investigación. El certificado de confidencialidad no le impide a usted o a un familiar suyo compartir información de manera voluntaria. De manera similar, si una compañía de seguros, empleador u otra persona obtiene su autorización por escrito para recibir información sobre la investigación, entonces los investigadores no pueden usar el certificado de confidencialidad para no entregar esa información.

Página de firmas para la obtención del consentimiento informado

Lo siguiente es una lista de los temas del estudio de investigación sobre los cuales hemos hablado. Si usted tiene alguna pregunta sobre alguno de estos temas, por favor pídale a la persona con la que está hablando sobre el estudio que le dé más información antes de aceptar participar en el estudio.

- De qué trata el estudio.
- Qué debo hacer cuando esté en el estudio.
- Los posibles riesgos y beneficios para mí.
- A quién contactar si tengo preguntas o si hay alguna lesión relacionada con el estudio.
- Información sobre costos y pagos.
- Puedo dejar de participar en el estudio en cualquier momento sin recibir ninguna sanción.
- Información sobre otras opciones.
- Toda información escrita y publicada se informará como datos grupales y no se hará mención a mi nombre.
- Me han dado el nombre del investigador y de otros para contactarlos.
- Tengo el derecho de preguntar cualquier duda.

Nombre en letra de imprenta del
participante

Firma del participante

Fecha

Nombre en letra de imprenta de la
persona que lleva a cabo el proceso
del consentimiento informado

Firma de la persona que lleva a
cabo el proceso del
consentimiento informad

Fecha

Nombre del intérprete

Firma del intérprete

Fecha

**ALBERT EINSTEIN COLLEGE OF MEDICINE OF YESHIVA UNIVERSITY
MONTEFIORE MEDICAL CENTER
Group 4 Consent Forms**

Individual Information and Consent Form

You are being asked to join this research study.

The title of the study is: Genetics of Lung Disease (Exhaled Breath Markers in Lung Carcinogenesis)

The study is being done under the supervision of:

Principal Investigator (Researcher Study Doctor): Simon Spivack M.D.

Office Address: Price Center 268 1301 Morris Park Avenue, Bronx, NY 10467

Telephone #: 718 678-1040

Protocol #: 2007-407-000

DO I HAVE TO TAKE PART IN THIS RESEARCH STUDY?

- Your participation is voluntary. This means that you decide whether or not you want to join the study after speaking with the researcher, or other member of the research team.
- If you decide to take part you will be asked to sign this consent form. Your signature means that you agree to be a subject in this research.
- After reading this form and having a discussion about what it says, you should ask all the questions you want to ask. You should take as much time as you need to make a decision.
- If you do not understand some of the terms used in this form, ask the person who is discussing the study with you to give any additional information that may make this easier to understand.
- You do not have to consent to participate in the study immediately, or ever. Take time to decide whether or not you wish to join. You may take home a copy of this consent form to think about it or discuss the information with family or friends before you decide.
- If you decide not to participate, the care providers at this facility will give you all of the standard care that is appropriate for you.
- You will be given a copy of this form whether or not you agree to participate in this study. Do not sign the form unless you have had all your questions answered and understand exactly what is involved.
- If you decide to take part you are still free to withdraw at any time without giving a reason. This will not affect your care and you will continue to be treated at this facility.
- The form discusses:
 - WHAT THE RESEARCHERS WILL LEARN FROM THE RESEARCH
 - WHAT WILL HAPPEN TO YOU DURING THE RESEARCH
 - WHAT RISKS AND/OR DISCOMFORTS YOU MIGHT EXPECT/EXPERIENCE AS A RESEARCH SUBJECT
 - IF YOU CAN EXPECT ANY BENEFITS, AND ARE THERE ANY ALTERNATIVES TO THIS RESEARCH FOR YOUR CONDITION.

WHY HAVE I BEEN ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being asked to take part in a research study:

- To examine the patterns of EBC DNA methylation (defined below) in HIV- infected individuals

WHY IS THIS RESEARCH STUDY BEING DONE?

- This research will attempt to establish a relationship between the molecular changes that occur in cells from the mouth, saliva, sputum, exhaled breath and blood as they relate to the development of lung disease. If this relationship can be proven, it may be possible in the future to test for certain lung diseases with a simple laboratory test.
- Dr. Simon Spivack, the principal investigator, is conducting a research investigation to determine whether the activity of certain genes and proteins in the lung and other tissues increases with exposure to cigarette smoke or environmental hazards. This increased activity might impact the development of lung disease. Genes instruct proteins to control and direct many activities of cells in the human body. The genes of interest to this investigation include inhaled foreign compound-processing genes, certain cancer-associated genes, and other genes, proteins and biological markers associated with the metabolism of foreign substances, cellular processes, and other lung disease related processes. The activity of genes and proteins found in the lung are thought to parallel that detected in blood, saliva, sputum, exhaled breath condensate (moisture) and mouth cells. This is unproven. Additionally, the relationship of these genes' activity to lung diseases, including lung cancer, remains unproven.
- To examine the stability of EBC DNA methylation patterns over time in HIV- infected smokers.

HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

You will be one of approximately 500 who will be participating in this study at Montefiore Medical Center and Albert Einstein College of Medicine.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

We expect that you will be in this research study from the time informed consent is signed until you complete the interview process and specimen collection (30 minutes). PROCEDURES:

- You will be asked to complete a questionnaire containing questions about environmental exposures, medication and family history. The questionnaire takes about 15 minutes to complete. The research staff will be available to assist you as needed.
- Participants will also undergo exhaled carbon monoxide testing using the Bedfont piCO Smokerlyzer at baseline in order to confirm smoking status. You will be asked to take a deep breath, hold it for 15 seconds, and then breathe out into the mouthpiece of the Smokerlyzer machine. If you are uncomfortable holding your breath for 15 seconds, you may breathe into the mouthpiece as soon as you begin to feel uncomfortable.
- A collection of saliva will be collected by spitting into a cup.
- A collection of your exhaled breath condensate (EBC). This will be done by having you rinse your mouth with water and then breathing normally into a disposable portable mouthpiece for 15 minutes to collect 1 ml (less than one quarter teaspoon) of EBC. It may be necessary to wear a nose clip during the collection. Specimen collection takes about 20-30 minutes. You may be asked to return for a second, identical collection of EBC 3 to 6 months after the initial collection. If you agree to the second collection, you will receive compensation for your time and effort as described below.

ADDITIONAL TESTS ON YOUR SAMPLE: In the future because of the acquisition of new knowledge through research and advances in techniques in the field of genetic testing, the

investigator may wish to conduct other biologic and genetic testing focused solely on the susceptibility to lung cancer and other lung diseases caused by inhaled toxins, or other substances. This gives consent for possible further testing on your specimens. The additional tests would be focused on foreign compound-processing genes, cancer-associated genes and other genes, proteins and biologic markers associated with the metabolism of foreign substances, cellular function, and other lung disease- relevant phenomena. All previously mentioned assurances for your confidentiality will be maintained. The results of all genetic testing will not be made available to you. If you would like to speak with a genetics counselor about general information concerning the storage of genetic specimens, you may call one.

- Since the significance of these tests are not known for you, we will not disclose the results of the genetic testing. No formal counseling will be provided under the research study. If you request, you will be referred to a genetic counselor. You or your insurance carrier will be responsible for the genetic counselor's fee.

WILL THIS STUDY INVOLVE GENETIC RESEARCH and/or TESTING

This research study is designed to explore the genes and molecules that may be responsible for the susceptibility and/or development of lung disease in anticipation of establishing molecular screening strategies for the early detection of lung diseases, including cancer.

- Tests conducted under this research study may reveal genetic information.
- **GENETIC COUNSELING INFORMATION:** You may wish to obtain professional genetic counseling prior to signing the informed consent. A genetic counselor is a person qualified to provide information about what the results of this type of test may mean to you and your family. You or your insurance company will be responsible for the cost of these services.

WHAT ARE THE POSSIBLE SIDE EFFECTS, DISCOMFORTS, RISKS OR INCONVENIENCES I CAN EXPECT FROM BEING IN THIS RESEARCH STUDY?

Here is a list of the known risks associated with this research:

- **Questionnaire:** Occasionally, the discussion about smoking history or environmental contaminant exposure during the interview process may provoke anxiety.
- **Saliva:** This is a non-invasive test and does not have any known risk.
- **Exhaled breath condensate:** collection is a non-invasive test and does not have any known risk. You may feel uncomfortable from breathing into a tube and possibly wearing a nose clip for 10-15 minutes.
- **Exhaled carbon monoxide testing:** This is a non-invasive test and does not have any known risks. You may feel uncomfortable while holding your breath for 15 seconds. If so, you may exhale into the mouthpiece as soon as you begin to feel uncomfortable.

WILL THE RESULTS OF THIS STUDY OR ANY OF THE PROCEDURES AFFECT MY INSURABILITY?

The tests done under this study will not affect your ability to get or keep medical, health or life insurance.

ARE THERE LIKELY TO BE ANY BENEFITS TO TAKING PART IN THIS RESEARCH STUDY?

You will not benefit from being in this research study. However, there may be a general benefit to society by the furthering of scientific knowledge. The information gained by using your saliva and exhaled breath condensate will help us better understand lung disease and help us establish molecular screening strategies for the early detection of lung disease and lung cancer.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS RESEARCH STUDY?

You may choose not to participate in this study.

WILL I BE PAID FOR BEING IN THE STUDY?

You will receive \$20 to compensate you for your time and effort. If you are asked to return for a second EBC collection, and agree to do so, you will receive an additional \$20 to compensate you for your time and effort.

WHO MAY SEE MY RECORDS?

The research records will be kept private and your name will not be used in any written or verbal reports.

- Your research records and medical records may be inspected by members of the research team and other institutions that participate in this study. These are: The U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), Department of Health and Human Services (DHHS) offices, New York State Department of Health (NYSDOH), Governmental agencies in other countries, Federal agencies involved with research, governmental agencies to whom certain diseases (reportable diseases) must be reported.
- The researcher and research staff will review your medical records and will keep the information private.
- The research records will be kept in a secured manner and computer records will be password protected.
- The people who reviewed this research study as members of the Albert Einstein College of Medicine Committee on Clinical Investigations (CCI) and the Montefiore Medical Center Institutional Review Board (IRB) may also review your research and medical records.
- The Office of Human Research Protections (OHRP) may also review your research study records.
- The research records will be kept in a secured manner and computer records will be password protected in the Albert Einstein College of Medicine Clinical Research Center (CRC).
- The Clinical Research Center staff, as well as the research personnel authorized by the researcher will have access to these records.
- All of these groups have been requested to keep your name private.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

If there is a physical injury as a result of this research, only immediate, essential, short-term medical treatment as determined by the participating hospital, will be available for the injury without charge to you personally.

- No monetary compensation will be offered.

- You are not waiving any of your legal rights by signing this informed consent document
- If additional treatment is required as a result of a physical injury related to the research, necessary medical treatment will be provided to you and billed to your insurance company or to you as part of your medical expenses.

Immediately report any discomforts, problems or injuries you experience during the course of your participation in the study to Dr. Simon Spivack at 718 678-1040 between the hours of 9am to 5pm.

WILL THERE BE ANY COSTS TO ME?

There will be no costs to you for participating in this study.

CAN I BE ASKED TO STOP PARTICIPATING IN THIS STUDY BEFORE THE STUDY IS FINISHED?

If the study goal has been reached, you can be asked to stop participating.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

Researcher's Name: Dr. Simon Spivack

Office Address: 1301 Morris Park Avenue Price Center 268 Bronx, NY 10467

Office Phone: 718-678-1040

- If any questions arise related to this research project, or you believe you have any injury related to this study; you can call the researcher above.
- If you have questions regarding your rights as a research subject, you may also call the Manager of The Albert Einstein College of Medicine Committee on Clinical Investigations at (718) 430-2253, Monday through Friday between 9 AM and 5 PM.

WILL ANY OF THE SAMPLES (BLOOD, TISSUE, DNA) TAKEN FROM ME BE USED FOR FUTURE RESEARCH STUDIES?

USE OF DE-IDENTIFIED SPECIMENS FOR FUTURE RESEARCH:

In addition to the research you are consenting to under this research study, *Dr. Simon Spivack* or other researchers at this or other institutions may wish to study the samples in future research, including genetic analysis. These samples, taken from your body, would NOT be linked back to you. No one will know your name or protected health information.

At this time, the researcher does not know what the future studies will be. Your specimens may also be submitted to a tissue/cell/DNA bank. The specimens may be kept for a long time and may exceed 50 years.

In some research using human blood or tissue, the specimens and their parts may enable researchers to develop medical tests or treatments that have commercial value. You will not receive any money that may result from any such commercial tests or treatments.

Your specimens may be used for future research, even though the purpose of the future research is not known at this time.

PARTICIPANT:**PLEASE INDICATE YOUR CHOICE BY INITIALING ONE (1) OF THE FOLLOWING OPTIONS**

I consent to have my specimens used for future research studies.

I consent to have my specimens used for future research studies only for the study of _____

I do NOT consent to have my specimens used for future research studies. (The specimens will be destroyed at the end of the study.)

WHAT IF NEW INFORMATION BECOMES AVAILABLE?

- If the research study doctor obtains new information that might lead you to change your mind about continuing in this study, the research study doctor will tell you about it.
- If you decide to withdraw, the research study doctor and your personal doctor will make arrangements for your care to continue.

MAY I STOP THE STUDY AT ANY TIME?

- Your participation in this study is voluntary, and you may withdraw from the study at any time without giving a reason.
- If you agree to participate and withdraw at a later time, some of your information may have already been entered into the study and that will not be removed.
- In addition, you may be asked to return to the research study doctor again for any final tests in order to close the record and tests or monitoring that are necessary for your health as a result of your participation. These results may be recorded.
- Your treatment by doctors and staff at the institution(s) involved in this study, now and in the future, will not be affected in any way if you agree to participate and withdraw later.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS RESEARCH STUDY?

- Your participation in this study is voluntary.
- You do not waive any of your legal rights by participating in this research study.

Your treatment by doctors and staff at the institution(s) involved in this study, now and in the future, will not be affected in any way if you refuse to participate or if you enter the study and withdraw later.

Disclosure: The PI, Dr. Simon Spivack, has applied for a patent on a specific way of testing for DNA methylation (changes) called GC-tagged Bisulfite Genomic Sequencing. Based on data from this and other research, royalties and other compensation may be received by the institution and the PI. Thus, the Institution and the PI have a potential financial interest in the outcome of this study

CERTIFICATE OF CONFIDENTIALITY

As a way to protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health, which is funding this study. If information from this study was requested or subpoenaed by government agencies or the courts, we will use the Certificate to attempt to legally refuse to provide it. This is rare – in only a few cases did researchers have to use the Certificate, and it was honored most of the time, but not every time. There are several kinds of situations that the Certificate does not apply. For example, we are still required to report child abuse and some diseases, and we must make data available to the government for a review or evaluation of our research. The Certificate does not prevent you or a member of your family from voluntarily sharing information. Similarly, if an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information

INFORMED CONSENT SIGNATURE PAGE

The following is a list of items we discussed about this research study. If you have any questions about any of these items, please ask the person who is discussing the study with you for more information before agreeing to participate.

- What the study is about.
- What I must do when I am in the study.
- The possible risks and benefits to me.
- Who to contact if I have questions or if there is a research related injury.
- Any costs and payments.
- I can discontinue participating in the study at any time without penalty.
- Other choices.
- All written and published information will be reported as group data with no reference to my name.
- I have been given the name of the researcher and others to contact.
- I have the right to ask any questions.

PRINTED NAME OF PARTICIPANT

SIGNATURE OF PARTICIPANT

DATE

PRINTED NAME OF PERSON
CONDUCTING THE INFORMED
CONSENT PROCESS

SIGNATURE OF PERSON
CONDUCTING THE INFORMED
CONSENT PROCESS

DATE

**ALBERT EINSTEIN COLLEGE OF MEDICINE OF YESHIVA UNIVERSITY
MONTEFIORE MEDICAL CENTER**

Individual Information and Consent

Form, Group 5, Bronchoscopy 9-15

You are being asked to join this research study.

The title of the study is: Genetics of Lung Disease (Exhaled Breath Markers in Lung Carcinogenesis)

The study is being done under the supervision of:

Principal Investigator (Researcher Study Doctor): Simon Spivack M.D.

Office Address: 1301 Morris Park Avenue, Price Center Rm 268
Bronx, NY 10467

Telephone#: 718 678-1040

Protocol #: 2007-407-000

Disclosure: The PI, Dr.Simon Spivack, has received a patent on a specific way of testing for DNAmethylation(changes) called GC-tagged Bisulfite Genomic Sequencing. This method is being used in the current study. Based on data from this and other research, the potential financial value of this testing method may be increased. Thus, the Institution and the PI have a potential financial interest in the outcome of this study.

DO I HAVE TO TAKE PART IN THIS RESEARCH STUDY?

- Your participation is voluntary. This means that you decide whether or not you want to join the study after speaking with the researcher, or other member of the research team.
- If you decide to take part you will be asked to sign this consent form. Your signature means that you agree to be a subject in this research.
- After reading this form and having a discussion about what it says, you should ask all the questions you want to ask. You should take as much time as you need to make a decision.
- If you do not understand some of the terms used in this form, ask the person who is discussing the study with you to give any additional information that may make this easier to understand.
- You do not have to consent to participate in the study immediately, or ever. Take time to decide whether or not you wish to join. You may take home a copy of this consent form to think about it or discuss the information with family or friends before you decide.
- If you decide not to participate, the care provider at this facility will give you all of the standard care that is appropriate for you.
- You will be given a copy of this form whether or not you agree to participate in this study. Do not sign the form unless you have had all your questions answered and understand exactly what is involved.
- If you decide to take part you are still free to withdraw at any time without giving a reason. This will not affect your care and you will continue to be treated at this facility.
- The form discusses:
 - WHAT THE RESEARCHERS WILL LEARN FROM THE RESEARCH
 - WHAT WILL HAPPEN TO YOU DURING THE RESEARCH

- WHAT RISKS AND/OR DISCOMFORTS YOU MIGHT EXPECT/EXPERIENCE AS A RESEARCH SUBJECT
- IF YOU CAN EXPECT ANY BENEFITS, AND ARE THERE ANY ALTERNATIVES TO THIS RESEARCH FOR YOUR CONDITION.

WHY HAVE I BEEN ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being asked to take part in a research study because you will soon be having a bronchoscopy for a clinical reason (your medical care).

WHY IS THIS RESEARCH STUDY BEING DONE?

- This research will attempt to establish a relationship between the molecular changes that occur in cells from the mouth, saliva, sputum, exhaled breath and blood as they relate to the development of lung disease. If this relationship can be proven, it may be possible in the future to test for certain lung disease with a simpler laboratory test.
- Dr. Simon Spivack, the principal investigator, is conducting a research investigation to determine whether the activity of certain genes and proteins in the lung and other tissues increases with exposure to cigarette smoke or environmental hazards. This increased activity might impact the development of lung disease. Genes instruct proteins to control and direct many activities of cells in the human body. The genes of interest to this investigation include inhaled foreign compound-processing genes, certain cancer-associated genes, and other genes, proteins and biological markers associated with the metabolism of foreign substances, cellular function, and other lung disease-related processes. The activity of genes and proteins found in the lung are thought to possibly parallel that detected in blood, saliva, exhaled breath condensate (moisture) and mouth cells. This is unproven. Additionally, the relationship of these genes' activity to lung diseases, including lung cancer, remains unproven.

HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

You will be one of approximately 2000 who will be participating in this study at Montefiore Medical Center and Albert Einstein College of Medicine.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

If you agree, we will tell you more about the study and answer any questions you may have before your bronchoscopy procedure.

We expect that you will be in this research study from the time informed consent is signed until you complete your bronchoscopy.

The interview process and specimen collection takes approximately 55 minutes.

PROCEDURES:

- Bronchoscopy procedure: With your consent, and with the approval of the physician performing the standard and fluorescent bronchoscopy, we would like to perform several

additional collections. First, a broncho alveolar lavage (BAL) will be performed. A BAL is a procedure done during the bronchoscopy when five 20cc aliquots (each 20cc aliquot is equal to 4 teaspoons, equalling 20 teaspoons total) of sterile saltwater fluid is inserted into a small part of the lung and partially collected for examination.

- Second, after the procedure for clinical purposes is completed, checking that the patient is tolerating that procedure well, we will be taking 9-15 additional very small biopsy specimens, using tiny brushes. The small brushes are inserted through the bronchoscope. With your consent, your physician will use a brush to collect a tiny sample of lung tissue. This lung tissue and/or fluid from BAL will be compared to the blood, sputum, and other cells you may have donated. Analysis of the lung genes (DNA) or their products (RNA and proteins), will be performed by examining these small portions of lung tissue removed by your surgeon or pulmonologist during bronchoscopy. Each of these additional procedures will lengthen the time of your bronchoscopy procedure. If you agree to participate, this surgical tissue will be forwarded from the Surgeon and Department of Pathology at Montefiore Medical Center to Dr. Spivack and his research associates at the Price Center, Albert Einstein College of Medicine, Bronx, NY.
- You will be asked to complete a questionnaire regarding the amount you have smoked, your diet, other environmental exposures, medication and family history. This information is crucial to this study. The questionnaire will be administered by research nurse study staff and takes about 15 minutes to complete.
- There are six (6) specimens study staff would like to collect:
 - Extra tubes of blood (30 ml or about 2 tablespoons of blood) will be drawn at the same time as your clinically indicated pre-anesthesia blood tests or at the same time your IV is inserted prior to your bronchoscopy, to avoid extra needle sticks.
 - A collection of mouth cells by rinsing your mouth with an over-the-counter mouthwash solution.
 - A manual spinning of a brush will be held against the lining of each cheek four times to collect additional mouth cells.
 - A collection of your exhaled breath condensate (EBC). This will be done by having you inhale your mouth with water and then breathing normally into a disposable portable mouthpiece for 10-15 minutes to collect 1 ml (less than one quarter teaspoon) of EBC. It may be necessary to wear a nose clip during the collection.
 - A collection of your saliva, by spitting into a cup. A second collection of your saliva, obtained by chewing on a cotton-wool swab called a salivette for about 30 to 60 seconds, will be obtained. One can measure cotinine, reflective on smoking, in the saliva, in addition to other measurements.
 - A collection of your sputum (phlegm from your throat) will be collected by taking a deep breath and coughing sputum directly into a collection cup. If you are unable to collect sputum this way we may give you a saline nebulizer for 10 minutes to moisten the airway and then ask you to take a deep breath and cough sputum directly into a collection cup.
 - The six specimens are collected by research staff or phlebotomy staff.
 - Specimen collection takes about 20-30 minutes.

In addition, this consent gives permission to the investigator to obtain a copy of the pathology report for your lung tissue that is sent by your physician to pathology for diagnosis. These reports will not be sent with any information regarding your personal identity.

ADDITIONAL TESTS ON YOUR SAMPLE: In the future because of the acquisition of new knowledge through research and advances in techniques in the field of genetic testing, the investigator may wish to conduct other biologic and genetic testing focused solely on the susceptibility to lung cancer and other lung diseases caused by inhaled toxins, or other substances. This gives consent for possible further testing on your specimens. The additional tests would be focused on foreign compound-processing genes, cancer-associated genes and other genes, proteins and biologic markers associated with the metabolism of foreign substances, cellular function, and other lung disease- relevant phenomena. All previously mentioned assurances for your confidentiality will be maintained. The results of all genetic testing will not be made available to you. If you would like to speak with a genetics counselor about general information concerning the storage of genetic specimens, you may call one.

Since the significance of these tests are not known for you, we will not disclose the results of the genetic testing. No formal counseling will be provided under the research study. If your request, you will be referred to a genetic counselor. You or your insurance carrier will be responsible for the genetic counselor's fee.

WILL THIS STUDY INVOLVE GENETIC RESEARCH and/or TESTING

This research study is designed to explore the genes and molecules that may be responsible for the susceptibility and/or development of lung disease in anticipation of establishing molecular screening strategies for the early detection of lung diseases, including cancer.

- Tests conducted under this research study may reveal genetic information.
- **GENETIC COUNSELING INFORMATION:** You may wish to obtain professional genetic counseling prior to signing the informed consent. A genetic counselor is a person qualified to provide information about what the results of this type of test may mean to you and your family. You or your insurance company will be responsible for the cost of these services.

WHAT ARE THE POSSIBLE SIDE EFFECTS, DISCOMFORTS, RISK OR INCONVENIENCES I CAN EXPECT FROM BEING IN THIS RESEARCH STUDY?

Here is a list of the known risks associated with this research:

- **Questionnaire:** Occasionally, the discussion about smoking history or environmental contaminant exposure during the interview process may provoke anxiety.
- **Blood:** Rarely, is an extra needle stick required to collect the blood specimens. The risks involved in blood sampling are infection (rare) and bruising and pain (occasionally).
- **Mouth:** swabs with soft brushes rarely may cause discomfort and bleeding. The mouthwash solution causes a tingling sensation that resolves quickly and rarely is a cause for discomfort.
- **Exhaled breath condensate:** collection is a non-invasive test and does not have any known risk. You may feel uncomfortable from breathing into a tube and possibly wearing a nose clip for 10-15 minutes.
- **Saliva:** collection does not have any known risk.
- **Sputum:** The risk regarding the sputum induction include cough, fall in oxygen level in the blood, and bronchospasm (narrowing of the airway) especially in asthmatics.

BRONCHOSCOPY RISK:

Extra Procedures in Bronchoscopy:

For patients who have consented to have biopsies not needed for their clinical diagnosis, the incidence of minor to moderate bleeding is small (3 in 1000) and usually resolves spontaneously within minutes. The risk of increased bleeding that would require non-surgical treatment (medication called epinephrine will be applied topically to stop bleeding) is even smaller (less than 1 in 1000). The incidence of collapsed lung from endobronchial biopsy, requiring chest tube insertion to be placed to re inflate the lung, is expected to be much less than the 3 in 1000 estimated for trans bronchial biopsies, because the procedure is performed under direct visual guidance.

For patients having broncho-alveolar-lavage (BAL), there are no additional risks in up to 95% (95 in 100) of patients. Of the remaining ~5% (5 in 100), most complications are minor, and very brief, including transient (lasting seconds-minutes) decrease in base line blood oxygen (frequency approximately 2 in 100), fever of short duration (approximately 2 in 100), cough (approximately 1 in 100), chills of short duration (less than 1 in 100), bronchospasm (narrowing of the airway, in less than 1 in 100). Bronchospasm treatment includes supplemental oxygen and an inhaled aerosol medication given by nebulizer. Life-threatening complications occur very rarely, estimated as less than 1 in 10,000.

These bronchoscopy procedures may be uncomfortable and may extend (take a little longer to complete) the bronchoscopy (approximately 10-15 minutes), possibly requiring additional sedatives (medicine to help keep you comfortable).

Fluorescence bronchoscopy prolongs procedure duration for 5-8 minutes, there are no known additional risks.

WILL THE RESULTS OF THIS STUDY OR ANY OF THE PROCEDURES AFFECT MY INSURABILITY?

The tests done under this study will not affect your ability to get or keep medical, health or life insurance.

ARE THERE LIKELY TO BE ANY BENEFITS TO TAKING PART IN THIS RESEARCH STUDY?

You will not benefit from being in this research study. However, there may be a general benefit to society by the furthering of scientific knowledge. The information gained by using your tissues will help us better understand lung disease and help us establish molecular screening strategies for the early detection of lung disease and lung cancer.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS RESEARCH?

You may choose not to participate in this study.

WILL I BE PAID FOR BEING IN THE STUDY?

If you agree to take part in this research study, we will compensate (give) you for your time and expenses (\$5.00 each for 6 lab tests as outlined in procedure section and \$45.00 for bronchoscopy procedure for maximum amount of \$75.00).

If you do not complete the study, your payment will be prorated (adjusted). We will be collecting your social security number in order to process your payment.

WHO MAY SEE MY RECORDS?

- The research records will be kept private and your name will not be used in any written or verbal reports.
- Your research records and medical records may be inspected by members of the research team and other institutions that participate in this study. These are: The U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), Department of Health and Human Services (DHHS) offices, Governmental agencies in other countries, Federal agencies involved with research, governmental agencies to whom certain diseases (reportable diseases) must be reported.
- The researcher and research staff will review your medical records and will keep the information private.
- The research records will be kept in a secured manner and computer records will be password protected.
- The people who reviewed this research study as members of the Albert Einstein College of Medicine Committee on Clinical Investigations (CCI) and the Montefiore Medical Center Institutional Review Board (IRB) may also review your research and medical records.
- The Office of Human Research Protections (OHRP) may also review your research study records.
- The research records will be kept in a secured manner and computer records will be password protected in the Albert Einstein College of Medicine Clinical Research Center (CRC).
- The Clinical Research Center staff, as well as the research personnel authorized by the researcher will have access to these records.
- All of these groups have been requested to keep your name private.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

If there is a physical injury as a result of this research, only immediate, essential, short-term medical treatment as determined by the participating hospital, will be available for the injury without charge to you personally.

- No monetary compensation will be offered.
- You are not waiving any of your legal rights by signing this informed consent document
- If additional treatment is required as a result of a physical injury related to the research, necessary medical treatment will be provided to you and billed to your insurance company or to you as part of your medical expenses.

Immediately report any discomforts, problems or injuries you experience during the course of your participation in the study to Dr. Simon Spivack at 718 678-1040 between the hours of 9am to 5pm.

WILL THERE BE ANY COSTS TO ME?

There will be no costs to you for participating in this study.

CAN I BE ASKED TO STOP PARTICIPATING IN THIS STUDY BEFORE THE STUDY IS FINISHED?

If the study goal has been reached, you can be asked to stop participating.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

Researcher's Name: Dr. Simon Spivack

Office Address: 1301 Morris Park AvenuePriceCenter268Bronx, NY10467

Office Phone: 718-678-1040

- If any questions arise related to this research project, or you believe you have any injury related to this study, you can call the researcher above.
- If you have questions regarding your rights as are search subject, you may also call the Manager of The Albert Einstein College of Medicine Committee on Clinical Investigations at (718)430-2253, Monday through Friday between 9AM and 5 PM.

WILL ANY OF THE SAMPLES (BLOOD, TISSUE, DNA) TAKEN FROM ME BE USED FOR FUTURE RESEARCH STUDIES?**USE OF DE-IDENTIFIED SPECIMENS FOR FUTURE RESEARCH:**

In addition to the research you are consenting to under this research study, *Dr.SimonSpivack* or other researchers at this or other institutions may wish to study the samples in future research, including genetic analysis. These samples, taken from your body, would NOT be linked back to you. No one will know your name or protected health information.

At this time, the researcher does not know what the future studies will be Your specimens may also be submitted to a tissue/cell/DNA bank. The specimens may be kept for along time and may exceed 50years.

In some research using human blood or tissue, the specimens and their parts may enable researchers to develop medical tests or treatments that have commercial value. You will not receive any money that may result from any such commercial tests or treatments.

Your specimens may be used for future research, even though the purpose of the future research is not known at this time.

PARTICIPANT:**PLEASE INDICATE YOUR CHOICE BY INITIALING ONE (1) OF THE FOLLOWING OPTIONS**

I consent to have my specimens used for future research studies.

I consent to have my specimens used for future research studies only for the study of

___ I do NOT consent to have my specimens used for future research studies. (The specimens will be destroyed at the end of the study.)

WHAT IF NEW INFORMATION BECOMES AVAILABLE?

- If the research study doctor obtains new information that might lead you to change your mind about continuing in this study, the research study doctor will tell you about it.
- If you decide to withdraw, the research study doctor and your personal doctor will make arrangements for your care to continue.

MAY I STOP THE STUDY AT ANY TIME?

- Your participation in this study is voluntary, and you may withdraw from the study at any time without giving a reason.
- If you agree to participate and withdraw at a later time, some of your information may have already been entered into the study and that will not be removed.
- In addition, you may be asked to return to the research study doctor again for any final tests in order to close the record and tests or monitoring that are necessary for your health as a result of your participation. These results maybe recorded.
- Your treatment by doctors and staff at the institution(s)involved in this study, now and in the future, will not be affected in any way if you agree to participate and withdraw later.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS RESEARCH STUDY?

Your participation in this study is voluntary.

You do not waive any of your legal rights by participating in this research study.

Your treatment by doctors and staff at the institution(s)involved in this study, now and in the future, will not be affected in any way if you refuse to participate or if you enter the study and withdraw later.

CERTIFICATE OF CONFIDENTIALITY

As a way to protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health, which is funding this study. If information from this study was requested or subpoenaed by government agencies or the courts, we will use the Certificate to attempt to legally refuse to provide it. This is rare – in only a few cases did researchers have to use the Certificate, and it was honored most of the time, but not every time. There are several kinds of situations that the Certificate does not apply. For example, we are still required to report child abuse and some diseases, and we must make data available to the government for a review or evaluation of our research. The Certificate does not prevent you or a member of your family from voluntarily sharing information. Similarly, if an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Informed Consent Signature Page

The following is a list of items we discussed about this research study. If you have any questions about any of these items, please ask the person who is discussing the study with you for more information before agreeing to participate.

- What the study is about.
- What I must do when I am in the study.
- The possible risks and benefits to me.
- Who to contact if I have questions or if there is a research related injury.
- Any costs and payments.
- I can discontinue participating in the study at any time without penalty.
- Other choices.
- All written and published information will be reported as group data with no reference to my name.
- I have been given the name of the researcher and others to contact.
- I have the right to ask any questions.

Printed Name of Participant

Signature of Participant

Date

Printed Name of Person Conducting
The Informed Consent Process

Signature of Person Conducting
the Informed Consent Process

Date

**ALBERT EINSTEIN COLLEGE OF MEDICINE OF YESHIVA UNIVERSITY
MONTEFIORE MEDICAL CENTER**

Información para el participante y formulario de consentimiento

Grupo 5, Broncoscopia 9-15

Se le está pidiendo que participe en este estudio de investigación.

El nombre del estudio es: Genética de la enfermedad pulmonar (marcadores en aire exhalado en la carcinogénesis pulmonar)

El estudio se está llevando a cabo bajo la supervisión de:

Investigador principal (doctor del estudio de investigación): Simon Spivack, MD

Dirección de oficina: 1301 Morris Park Avenue, Price Center Rm 268 Bronx, NY 10467

Número de teléfono: 718-678-1040

Número de protocolo: 2007-407-000

Declaración: El investigador principal, Dr. Simon Spivack, ha recibido una patente de una forma específica de analizar la metilación (cambios) del ADN que se llama GC (guanina y citosina) etiquetada con la secuenciación genómica de bisulfito. Este método se está usando en el estudio actual. En base a los datos de ésta y otras investigaciones, puede ser que el posible valor económico de este método de prueba aumente. De esta manera, la institución y el investigador principal tienen un posible interés económico en el resultado de este estudio.

¿TENGO QUE PARTICIPAR EN ESTE ESTUDIO DE INVESTIGACIÓN?

- Su participación es voluntaria. Esto quiere decir que usted decide si quiere participar el estudio o no después de hablar con el investigador, u otro miembro del equipo de investigación.
- Si decide participar en el estudio, le pediremos que firme este formulario de consentimiento. Su firma significa que usted acepta ser participante en esta investigación.
- Después de que usted lea este formulario y haya hablado sobre lo que trata el formulario, usted debe preguntar todo lo que quiere saber. Debe tomarse el tiempo que necesite antes de tomar una decisión.
- Si no entiende algunas de las palabras que se usan en este formulario, pídale a la persona con la que usted está hablando sobre el estudio que le dé información adicional que le permita entender más fácilmente.
- Usted no tiene que aceptar participar en el estudio ahora o en el futuro. Tómese su tiempo para decidir si desea participar o no. Usted puede llevarse una copia de este formulario de consentimiento para que lo piense o pueda comentar la información a su familia o sus amistades antes de tomar una decisión.
- Si usted decide no participar, los proveedores de atención médica en este centro le brindarán toda la atención médica habitual apropiada para usted.
- A usted se le dará una copia de este formulario, ya sea si acepta participar o no en este estudio. No firme el formulario a menos que le hayamos respondido a todas sus preguntas y entienda exactamente de lo que trata el estudio.

- Si decide participar en el estudio, todavía tiene la libertad de retirarse del estudio en cualquier momento sin tener que dar ninguna explicación. El retirarse del estudio no afectará su atención médica y usted continuará su tratamiento en este centro.
- El formulario trata sobre:
 - LO QUE LOS INVESTIGADORES SABRÁN DE LA INVESTIGACIÓN.
 - LO QUE LE PASARÁ A USTED DURANTE LA INVESTIGACIÓN.
 - LOS RIESGOS Y/O LAS MOLESTIAS QUE PUEDE ESPERAR/PRESENTAR COMO PARTICIPANTE DE LA INVESTIGACIÓN.
 - SI USTED PUEDE RECIBIR ALGÚN BENEFICIO, Y SI ¿HAY ALGUNA ALTERNATIVA A ESTA INVESTIGACIÓN PARA SU ENFERMEDAD?

¿POR QUÉ ME HAN PEDIDO QUE PARTICIPE EN ESTE ESTUDIO DE INVESTIGACIÓN?

Le estamos pidiendo que participe en el estudio de investigación porque pronto usted tendrá una broncoscopia por un motivo clínico (su atención médica).

¿POR QUÉ SE ESTÁ HACIENDO ESTE ESTUDIO DE INVESTIGACIÓN?

- Esta investigación tratará de establecer la relación entre los cambios moleculares que ocurren en las células de la boca, la saliva, el esputo, el aire exhalado y la sangre en relación al desarrollo de la enfermedad pulmonar. Si esta relación se puede probar, puede ser posible que en el futuro se hagan pruebas para detectar cierta enfermedad pulmonar con una prueba de laboratorio más simple.
- El Dr. Simon Spivack, el investigador principal, es el que está llevando a cabo la investigación para determinar si la actividad de ciertos genes y proteínas en el pulmón y en otros tejidos aumenta con la exposición al humo del cigarrillo o a los peligros ambientales. El incremento de esta actividad puede tener un efecto en el desarrollo de la enfermedad pulmonar. Los genes ordenan a las proteínas a controlar y dirigir muchas actividades de las células en el cuerpo humano. Los genes que son de interés para esta investigación incluyen los genes de procesamiento de compuestos extraños inhalados, ciertos genes relacionados con el cáncer y otros genes, marcadores proteínicos y biológicos relacionados con el metabolismo de sustancias extrañas, función celular y otros procesos relacionados con la enfermedad pulmonar. Se cree que la actividad de los genes y las proteínas encontradas en los pulmones son posiblemente iguales a aquella detectada en la sangre, la saliva, el condensado de aire exhalado (humedad) y las células de la boca. Esto no está probado. Además, la relación de la actividad de estos genes con las enfermedades pulmonares, incluyendo el cáncer de pulmón, continúa sin probarse.

¿CUÁNTAS PERSONAS PARTICIPARÁN EN ESTE ESTUDIO DE INVESTIGACIÓN?

- Usted será una(o) de aproximadamente 2 000 personas que estarán participando en este estudio en el Centro Médico Montefiore (*Montefiore Medical Center*) y en la Escuela de Medicina Albert Einstein (*Albert Einstein College of Medicine*).

¿QUÉ SUCEDERÁ SI PARTICIPO EN ESTE ESTUDIO DE INVESTIGACIÓN?

Si usted decide participar, le diremos más sobre el estudio y responderemos cualquier pregunta que tenga antes de su procedimiento de broncoscopia.

Esperamos que usted participe en este estudio de investigación desde el momento que usted firme el consentimiento informado hasta que complete la broncoscopia.

El proceso de la entrevista y la recolección de muestras toman unos 55 minutos.

PROCEDIMIENTOS:

- Procedimiento de broncoscopia: Con su consentimiento, y con la aprobación del médico que realiza la broncoscopia estándar y fluorescente, deseáramos hacer varias recolecciones adicionales. Primero, se le hará un lavado broncoalveolar (LBA). El lavado broncoalveolar es un procedimiento que se hace durante la broncoscopia cuando cinco alícuotas de 20 cc (cada alícuota de 20 cc es igual a 4 cucharaditas, equivalente a un total de 20 cucharaditas) de solución de agua salina estéril se introduce en una parte pequeña del pulmón y se recolecta parcialmente para su análisis. Segundo, después de completar el procedimiento para propósitos clínicos, verificando de que el paciente está tolerando el procedimiento bien, tomaremos de 9 a 15 muestras adicionales de biopsia muy pequeñas, usando cepillitos pequeños. Estos cepillitos se introducen a través del broncoscopio. Con su consentimiento, su médico usará un cepillo para recolectar una muestra muy pequeña de tejido pulmonar. Este tejido pulmonar y/o líquidos del lavado broncoalveolar se compararán con la sangre, el esputo, y otras células que usted pueda haber donado. Los análisis de los genes pulmonares (ADN) o de sus productos (ARN y proteínas) se harán examinando estas pequeñas porciones de tejido pulmonar que su cirujano o pulmonólogo extirpó durante la broncoscopia. Cada uno estos procedimientos adicionales aumentarán el tiempo del procedimiento de la broncoscopia. Si acepta participar, este tejido quirúrgico se enviará del cirujano y del Departamento de Patología del Centro Médico Montefiore al Dr. Spivack y a sus asociados de investigación en el Centro Price (*Price Center*, por su nombre en inglés), en la Escuela de Medicina Albert Einstein, Bronx, NY.
- Le pediremos que complete un cuestionario sobre la cantidad de cigarrillos que ha fumado, los alimentos que come, otras exposiciones ambientales, medicamentos, y antecedentes familiares. Esta información es de suma importancia para este estudio. Un(a) enfermero(a) de investigación del personal del estudio le tomará el cuestionario y durará cerca de 15 minutos completarlo.
- El personal del estudio recolectará seis (6) muestras:
 - Se le extraerán tubitos adicionales de sangre (30 mililitros o unas 2 cucharadas de sangre) al mismo tiempo que se le hagan las pruebas de sangre preanestésicas por indicación clínica o al mismo tiempo que se le introduzca la vía intravenosa antes de la broncoscopia, para evitar pinchazos de agujas adicionales.
 - Se recolectarán células de la boca enjuagándose la boca con una solución de enjuague bucal que es sin receta médica.
 - Se recolectarán células de la boca adicionales sosteniendo cuatro veces un cepillo suave de uso manual contra el revestimiento de cada mejilla.
 - Se recolectará una muestra de condensado de aire exhalado (CAE). Esta muestra se le tomará por medio del enjuague de la boca con agua y luego respirará normalmente en una boquilla portátil descartable de 10 a 15 minutos para recolectar 1 mililitro (menos

- de un cuarto de cucharadita) de condensado de aire exhalado. Pueda que sea necesario usar una pinza nasal durante la recolección de la muestra.
- Se recolectará una muestra de su saliva, tendrá que escupir en un vasito. Se recolectará una segunda muestra de su saliva la cual se obtendrá masticando un hisopo de algodón que se llama salivette de 30 a 60 segundos. Uno puede medir la cotinina, que se refleja al fumar, en la saliva, aparte de otras medidas.
 - Se recolectará una muestra de esputo (flema de la garganta). Respirará profundamente y toserá el esputo directamente en el vaso para la muestra. Si usted no puede recolectar el esputo de esta manera, podemos darle un nebulizador salino por 10 minutos para humedecer las vías respiratorias y luego le pediremos que respire profundamente y tosa el esputo directamente en el vaso para la muestra.

El personal de la investigación o el personal de flebotomía recolectarán las seis muestras.

La recolección de las muestras dura de unos 20 a 30 minutos.

Además, este consentimiento da permiso al investigador para obtener una copia del informe de patología del tejido pulmonar de usted que su médico envía a patología para el diagnóstico. Estos informes no se enviarán con ninguna información sobre su identificación personal.

- PRUEBAS ADICIONALES A SU MUESTRA: En el futuro debido al descubrimiento de nuevos conocimientos a través de investigaciones y avances en técnicas en el campo del análisis genético, el investigador puede querer hacer otros análisis biológicos y genéticos enfocados solamente en la susceptibilidad al cáncer de pulmón y a otras enfermedades pulmonares causadas por las toxinas exhaladas u otras sustancias. Esto da consentimiento para realizar posibles análisis posteriores a sus muestras. Los análisis adicionales se enfocarán en los genes de procesamiento de compuestos extraños, genes relacionados con el cáncer y otros genes, marcadores proteínicos y biológicos relacionados con el metabolismo de sustancias extrañas, función celular y otros fenómenos relevantes a la enfermedad pulmonar. Se mantendrán todas las garantías mencionadas anteriormente para su confidencialidad. No estarán disponibles para usted los resultados de todos los análisis genéticos. Si usted desea hablar con un consejero genético sobre información general relacionada al almacenamiento de las muestras genéticas, puede llamar a un consejero genético.
- Como usted no sabe el efecto de estos análisis, nosotros no revelaremos los resultados de los análisis genéticos. No se ofrecerá consejería oficial para este estudio de investigación. Si usted pide consejería, se le referirá a un consejero genético. Usted o su compañía de seguro médico serán responsables de los costos del consejero genético.

¿INVOLUCRARÁ ESTE ESTUDIO INVESTIGACIÓN GENÉTICA y/o ANÁLISIS GENÉTICOS?

Este estudio de investigación está diseñado para la exploración de genes y moléculas que pueden ser responsables de la susceptibilidad y/o desarrollo de la enfermedad pulmonar anticipándose al establecimiento de las estrategias de detección molecular para la detección temprana de las enfermedades pulmonares, incluyendo el cáncer.

- Las pruebas que se realicen para este estudio de investigación pueden revelar información genética.

- **INFORMACIÓN SOBRE CONSEJERÍA GENÉTICA:** Usted puede querer consejería genética antes de firmar el consentimiento informado. Un consejero genético es una persona calificada para dar información sobre lo que pueden significar los resultados de este tipo de análisis para usted y su familia. Usted o su compañía de seguro serán responsables de los costos de estos servicios.

¿CUÁLES SON LOS POSIBLES EFECTOS SECUNDARIOS, MOLESTIAS, RIESGOS O INCONVENIENTES QUE PUEDO ESPERAR AL PARTICIPAR EN ESTE ESTUDIO DE INVESTIGACIÓN?

Aquí hay una lista de los riesgos conocidos relacionados con esta investigación:

- **Cuestionario:** Algunas veces, el hablar sobre el historial del tabaquismo o la exposición a contaminantes ambientales durante la entrevista puede producirle ansiedad.
- **Sangre:** Raras veces, se necesita un pinchazo adicional para recolectar muestras de sangre. Los riesgos involucrados en la obtención de la muestra de sangre son infección (poco frecuente), y moretón y dolor (a veces).
- **Boca:** Los hisopos con cepillos suaves raras veces causan molestias y sangrado. La solución de enjuague bucal causa una sensación de cosquilleo que desaparece rápidamente y en raras ocasiones causa molestia.
- **Condensado de aire exhalado:** La recolección del condensado de aire exhalado es una prueba no invasiva y no tiene ningún riesgo conocido. Usted puede sentir incomodidad al respirar en un tubo y posiblemente usar una pinza nasal de 10 a 15 minutos.
- **Saliva:** La recolección de la saliva no tiene ningún riesgo conocido.
- **Espujo:** El riesgo relacionado con la provocación del espujo incluye tos, disminución del nivel de oxígeno en la sangre, y broncoespasmos (estrechez de las vías respiratorias) en especial en personas con asma.

RIESGO DE LA BRONCOSCOPIA:

Procedimientos adicionales en la broncoscopia:

Para los pacientes que han dado su consentimiento para hacerse biopsias que no son necesarias para sus diagnósticos clínicos, la incidencia de sangrado leve a moderado es pequeña (3 de cada 1 000), y por lo general se resuelve por sí solo en unos minutos. El riesgo del aumento del sangrado que necesitaría tratamiento no quirúrgico (medicamento llamado epinefrina se aplicará por vía tópica para parar el sangrado) es aún menor (menos de 1 de cada 1 000). La incidencia de pulmón colapsado a causa de la biopsia endobronquial, que requiere la inserción del tubo torácico para expandir el pulmón, se espera que sea mucho menor de 3 de cada 1 000 aproximado para las biopsias transbronquiales, porque el procedimiento se hace bajo guía visual directa.

Para los pacientes que se someten a un lavado broncoalveolar (LBA), no existen riesgos adicionales en hasta 95 % (95 de cada 100) de los pacientes. Del ~5 % restante (5 de cada 100), la mayoría de las complicaciones son leves y de corto tiempo, incluyendo descenso transitorio (que dura segundos-minutos) en los valores iniciales del oxígeno en la sangre (frecuencia aproximadamente 2 de cada 100), fiebre de corta duración (aproximadamente 2 de cada 100), tos (aproximadamente 1 de cada 100), escalofríos de corta duración (menos de 1 de cada 100), broncoespasmo (estrechez de las vías respiratorias, en menos de 1 de cada 100). El tratamiento para el broncoespasmo incluye oxígeno suplementario y un medicamento en aerosol por vía

inhalatoria administrado a través de un nebulizador. Muy raras veces ocurren complicaciones potencialmente mortales, estimadas en menos de 1 de cada 10 000.

Estos procedimientos de broncoscopia pueden ser incómodos y pueden extender (tomar un poco más de tiempo para terminar) la broncoscopia (aproximadamente de 10 a 15 minutos), pueda que requiera sedantes adicionales (medicina que le ayuda a tener comodidad durante el procedimiento). La broncoscopia fluorescente prolonga la duración del procedimiento de 5 a 8 minutos, no hay riesgos adicionales conocidos.

¿AFECTARÁN LOS RESULTADOS DE ESTE ESTUDIO O CUALQUIERA DE LOS PROCEDIMIENTOS LA OBTENCIÓN DE SEGURO MÉDICO?

Las pruebas que se realizan para este estudio no afectarán su capacidad obtener o conservar su seguro médico, seguro de salud o seguro de vida.

¿ES POSIBLE QUE HAYA ALGÚN BENEFICIO AL PARTICIPAR EN ESTE ESTUDIO DE INVESTIGACIÓN?

Usted no se beneficiará al participar en este estudio de investigación. Sin embargo, puede haber un beneficio general para la sociedad al fomentar el conocimiento científico. La información que se obtenga del uso de sus tejidos nos ayudará a entender mejor la enfermedad pulmonar y nos ayudará a establecer las estrategias de detección molecular para la detección temprana de la enfermedad pulmonar y el cáncer de pulmón.

¿QUÉ OTRAS OPCIONES TENGO SI NO PARTICIPO EN ESTE ESTUDIO DE INVESTIGACIÓN?

Usted puede elegir no participar en este estudio.

¿ME PAGARÁN POR PARTICIPAR EN EL ESTUDIO?

- Si decide participar en este estudio de investigación, le recompensaremos (daremos) por su tiempo y sus gastos (\$5.00 por cada una de las 6 pruebas de laboratorio tal como se resume en la sección de procedimiento y \$45 por el procedimiento de la broncoscopia por una cantidad máxima de \$75.00).

Si no completa el estudio, su pago será de manera proporcional (pago modificado).

Le pediremos su número de seguro social para poder procesar su pago.

¿QUIÉNES PUEDEN VER MIS REGISTROS?

- Los registros de la investigación se mantendrán confidenciales y su nombre no se usará en ningún informe escrito o verbal.
- Sus registros de la investigación y sus expedientes médicos pueden ser examinados por los miembros del equipo de investigación y otras instituciones que participan en este estudio. Estas instituciones son: la Administración de Alimentos y Medicamentos de los Estados Unidos (*U.S. Food and Drug Administration, FDA*), los Institutos Nacionales de la Salud (*National Institutes of Health, NIH*), las oficinas del Departamento de Salud y Servicios Humanos (*Department of Health and Human Services, DHHS*), las agencias gubernamentales en otros países, las agencias federales involucradas en la investigación,

las agencias gubernamentales a las que se deben informar ciertas enfermedades (enfermedades de declaración obligatoria).

- El investigador y el personal de la investigación examinarán sus expedientes médicos y mantendrán la información confidencial.
- Los registros de la investigación se guardarán de manera segura y los registros computarizados se protegerán con una contraseña.
- Las personas que examinaron este estudio de investigación como miembros del Comité de Investigaciones Clínicas (*Committee on Clinical Investigations, CCI*) de la Escuela de Medicina Albert Einstein y la Junta de Revisión Institucional (*Institutional Review Board, IRB*) del Centro Médico Montefiore también pueden examinar sus registros de la investigación y sus expedientes médicos.
- La Oficina para la Protección de los Seres Humanos en la Investigación (*Office for Human Research Protections, OHRP*) también puede examinar sus registros del estudio de investigación.
- Los registros de la investigación se guardarán de manera segura y los registros computarizados se protegerán con una contraseña en el Centro de Investigaciones Clínicas (*Clinical Research Center, CRC*) de la Escuela de Medicina Albert Einstein.
- El personal del Centro de Investigaciones Clínicas, así como el personal de la investigación autorizado por el investigador tendrán acceso a estos registros.
- A todos estos grupos se les ha pedido mantener su nombre de manera confidencial.

¿QUÉ PASA SI ME LESIONO PORQUE PARTICIPÉ EN ESTE ESTUDIO DE INVESTIGACIÓN?

Si tiene alguna lesión física como resultado de esta investigación, el hospital participante solamente le proveerá tratamiento médico inmediato, esencial, y a corto plazo para la lesión, libre de costo para usted.

- No se le ofrecerá ninguna compensación monetaria.
- Usted no renuncia a ninguno de sus derechos legales al firmar este consentimiento informado.
- Si se requiere tratamiento adicional como resultado de una lesión física relacionada con la investigación, se le proveerá tratamiento médico necesario y la factura se enviará a su compañía de seguro o a usted como parte de sus gastos médicos.

Informe de inmediato cualquier molestia, dolencia o lesión que presente durante el curso de su participación en el estudio al Dr. Simon Spivack llamando al número 718-678-1040 de 9 a.m. a 5 p.m.

¿HABRÁ ALGÚN COSTO PARA MÍ?

- No habrá ningún costo para usted por participar en este estudio.

¿Se me puede pedir que deje de participar en este estudio antes de que el estudio termine?

Si se alcanza la meta del estudio, podemos pedirle que deje de participar en este estudio.

¿QUIÉN PUEDE RESPONDER A MIS PREGUNTAS SOBRE EL ESTUDIO?

Nombre del investigador: Dr. Simon Spivack

Dirección de oficina: 1301 Morris Park Avenue, Price Center 268 Bronx, NY 10467

Número de teléfono: 718-678-1040

- Si tiene alguna pregunta relacionada con este proyecto de investigación, o cree que tiene alguna lesión relacionada con este estudio, puede llamar al investigador que se nombra arriba.
- Si tiene alguna pregunta sobre sus derechos como participante de la investigación, también puede llamar al jefe del Comité de Investigaciones Clínicas de la Escuela de Medicina Albert Einstein al número telefónico (718) 430-2253, de lunes a viernes de 9 a.m. a 5 p.m.

¿SE USARÁ ALGUNA DE LAS MUESTRAS (SANGRE, TEJIDO, ADN) QUE SE ME TOMARON PARA ESTUDIOS DE INVESTIGACIÓN FUTUROS?

USO DE MUESTRAS NO IDENTIFICADAS PARA INVESTIGACIONES FUTURAS:

Además de la investigación a la que usted ha decidido participar por medio de este estudio de investigación, el Dr. Simon Spivack u otros investigadores en esta institución u otras instituciones puede(n) querer estudiar las muestras en investigaciones futuras, entre ellas análisis genéticos. Estas muestras, que se tomaron de su cuerpo, NO serán relacionadas con usted. Nadie sabrá su nombre ni su información médica protegida.

En este momento, el investigador no sabe cuáles serán los estudios futuros. Sus muestras también se pueden enviar a un banco de tejido/células/ADN. Las muestras se pueden guardar durante mucho tiempo y pueden exceder los 50 años.

En algunas investigaciones en las que se utilizan sangre o tejido humano, las muestras y las partes de estas muestras pueden permitir a los investigadores desarrollar pruebas médicas o tratamientos médicos que tengan valor comercial. Usted no recibirá ningún dinero que pueda resultar de alguna de tales pruebas comerciales o tratamientos.

Sus muestras se pueden usar para investigaciones futuras a pesar de que el propósito de la investigación futura no se conoce en este momento

PARTICIPANTE:

POR FAVOR INDIQUE SU ELECCIÓN ESCRIBIENDO SUS INICIALES (PRIMERA LETRA DE SU NOMBRE Y APELLIDO) EN UNA (1) DE LAS SIGUIENTES OPCIONES

_____ Doy mi consentimiento para que mis muestras se utilicen en estudios de investigación futuros.

_____ Doy mi consentimiento para que mis muestras se utilicen en estudios de investigación futuros solamente para el estudio de _____

_____ NO doy mi consentimiento para que mis muestras se utilicen en estudios de investigación futuros. (Las muestras serán destruidas al final del estudio).

¿QUÉ SUCEDERÁ SI INFORMACIÓN NUEVA SE HACE DISPONIBLE?

- Si el doctor del estudio de investigación obtiene información nueva que pueda hacerle cambiar de opinión sobre continuar en este estudio, el doctor del estudio de investigación se lo informará.
- Si usted decide retirarse del estudio, el doctor del estudio de investigación y su doctor personal harán arreglos para que su atención médica continúe.

¿PUEDO DEJAR DE PARTICIPAR EN EL ESTUDIO EN CUALQUIER MOMENTO?

- Su participación en este estudio es voluntaria, y puede dejar de participar en el estudio en cualquier momento sin tener que dar ninguna explicación.
- Si decide participar en el estudio y lo abandona después, parte de su información puede que ya se haya ingresado al estudio y eso no se podrá eliminar.
- Además, a usted se le puede pedir que regrese a ver al doctor del estudio de investigación nuevamente para hacer cualquier prueba final, y así cerrar el registro y las pruebas o el monitoreo que son necesarios para su salud como resultado de su participación. Estos resultados se pueden registrar.
- El tratamiento que recibe por parte de los doctores y del personal en la institución o las instituciones involucrada(s) en este estudio, no será afectado de ningún modo, ni ahora ni en el futuro, si usted acepta participar en este estudio y después lo abandona.

¿CUÁLES SON MIS DERECHOS SI PARTICIPO EN ESTE ESTUDIO DE INVESTIGACIÓN?

- Su participación en este estudio es voluntaria.
- Usted no renuncia a ninguno de sus derechos legales al participar en este estudio de investigación.
- El tratamiento que usted recibe por parte de los doctores y del personal en la institución o las instituciones involucrada(s) en este estudio, no será afectado de ningún modo, ni ahora ni en el futuro, si usted se niega a participar en este estudio o si ingresa al estudio y después lo abandona.

Certificado de confidencialidad

Con el fin de proteger su privacidad, hemos obtenido un certificado de confidencialidad de los Institutos Nacionales de la Salud de los Estados Unidos (*National Institutes of Health*), que es la que financia este estudio. Si la información de este estudio fuera solicitada u ordenada por una orden judicial por las agencias del gobierno o las cortes, usaremos este certificado para legalmente negarnos a proporcionar tal información. Esto es una situación poco probable - solamente en unas pocas ocasiones, los investigadores tuvieron que usar el certificado, y se respetó la mayor parte del tiempo, pero no siempre. Existen varios tipos de situaciones en las que el certificado no es aplicable. Sin embargo, se nos exige, por ejemplo, denunciar abuso infantil y algunas enfermedades, y debemos poner a disposición del gobierno la información para un análisis o una evaluación de nuestra investigación. El certificado de confidencialidad no le impide a usted o a un

familiar suyo compartir información de manera voluntaria. De manera similar, si una compañía de seguros, empleador u otra persona obtiene su autorización por escrito para recibir información sobre la investigación, entonces los investigadores no pueden usar el certificado de confidencialidad para no entregar esa información.

Página de firmas para la obtención del consentimiento informado

Lo siguiente es una lista de los temas del estudio de investigación sobre los cuales hemos hablado. Si usted tiene alguna pregunta sobre alguno de estos temas, por favor pídale a la persona con la que está hablando sobre el estudio que le dé más información antes de aceptar participar en el estudio.

- De qué trata el estudio.
- Qué debo hacer cuando esté en el estudio.
- Los posibles riesgos y beneficios para mí.
- A quién contactar si tengo preguntas o si hay alguna lesión relacionada con el estudio.
- Información sobre costos y pagos.
- Puedo dejar de participar en el estudio en cualquier momento sin recibir ninguna sanción.
- Información sobre otras opciones.
- Toda información escrita y publicada se informará como datos grupales y no se hará mención a mi nombre.
- Me han dado el nombre del investigador y de otros para contactarlos.
- Tengo el derecho de preguntar cualquier duda.

Nombre en letra de imprenta del Participante

Nombre en letra de imprenta del

Fecha

Nombre en letra de imprenta de la persona que lleva a cabo el proceso del consentimiento informado

Firma de la persona que lleva a cabo el proceso del consentimiento informado

Fecha

Nombre del intérprete

Firma del intérprete

Fecha

STUDY: GENETICS OF LUNG DISEASE

CCI#: 2007-407

PRINCIPAL INVESTIGATOR: DR. SIMON SPIVACK

TOTAL NUMBER OF SUBJECTS ENROLLED IN THE STUDY

1. AIM 1 (CASE-CONTROL):
 - 93 CASES + 94 CONTROLS = 187 SUBJECTS
(AT MONTEFIORE)
 - 11 CASES + 21 CONTROLS = 35 SUBJECTS
(AT VA HOSPITAL)

2. AIM 2 (COHORT NESTED CASE-CONTROL):
 - 3 CASES + 6 CONTROLS = 9 SUBJECTS
(EFFORTS BEING REDOUBLED)

Amendment Form (Version 31.0)

1.0 General Information

The version you are using is: August 2017

1.2 Study Information

Study Title:

Genetics of Lung Disease (Exhaled Breath DNA Methylation in Lung Carcinogenesis)

Principal Investigator:

Simon Spivack

Submission Reference #:

034816

1.3 Please click Save and Continue.

2.0 Amendment Information

2.1 Select the modifications being made below:

- Change in PI
- Change in key personnel and study contacts
- Changes to IRB Application
- Changes to or addition of new informed consent documents
- Changes to or addition of other study documents (protocol, investigator brochures, questionnaires, protocol, investigators brochure, recruitment materials, instruments, case report forms, study handouts or other miscellaneous documents)
- Adding external funding (grant application must be uploaded and the IRB application must be updated)

2.2 Provide a brief summary of the changes:

We would like to remove Dr. Steven Keller from our study.

If this is a sponsored amendment, and the sponsor has provided a document with a summary of changes, provide a summary of the **key changes in the space above (i.e., administrative changes to the protocol, corrected protocol regarding test X and updated the consent document accordingly, etc.). The IRB cannot accept "see attached". The IRB also cannot accept just a copy of the list of changes instead of a summary.*

***For the addition of key personnel, please also indicate whether the individual(s) added will be conducting the informed consent process.*

2.3 Provide a justification for the amendment.

Dr. Steven Keller left Montefiore medical center, so we would like to remove him from our study.

2.4 For an amendment generated by a study sponsor, provide the amendment version information, e.g. "Amendment #2 dated 11August2011".

This information will be used in the approval letter for the amendment.

2.5 Did the amendment originate from a drug company, a national study group, etc.? If "Yes," a copy of the correspondence must be attached to this amendment application.

Yes No

3.0 Change Key Personnel

3.1 Update study personnel using the form below:

The current list of Study Contact(s) for this study is listed below :
(if the list is blank, try clicking on "Refresh Constant Fields" in the upper right corner)

Simon Spivack, Mohammed Aldebagh, Dhruv g Patel

Note that only the PI and the Study Contact will receive IRIS communications and have full access to the study.
Please make sure that there are active personnel listed as Study Contact(s).

If applicable, please add the new Principal Investigator for the Study:		
If applicable, please select the new Research Staff personnel:		
A) Additional Investigators		
B) Research Staff		
If applicable, please add any new Study Contact:		
<hr/>		
If applicable, please add a new Faculty Advisor:		
If applicable, please select any existing Personnel you wish to remove:		
Keller, Steven M	Co-Investigator	

3.2 If you are submitting a change in PI note the following:

- The PI must have a **current Conflict of Interest (COI) disclosure** on file (see the Amendment Handbook in the Help Menu for details). Note: The submission will be denied if the PI does not have a current COI disclosure on file.
- The PI must have a **current CITI course** on file (see the Amendment Handbook in the Help Menu for details)
- Upload a copy of the **new PI's CV/resume** in the Study Documents section of the Amendment Form
- If necessary, upload a **revised consent document** with the new PI's name (select "Changes to or addition of new informed consent documents" on the Amendment Information page)
- Route the amendment form for approval by the new PI's **department chair**
- Route the amendment form for approval by the **new PI**.
- The **former PI** must sign off on the submission. If the former PI has left the institution, contact iris-support@einstein.yu.edu for assistance.

See the Amendment Form Handbook in the help menu (orange and white question mark in the upper right corner) for further details on submitting these items.

3.3 If you are submitting a change in Additional Investigators note the following:

- Have a current **Conflict of Interest (COI) disclosure** on file (see the Amendment Handbook in the Help Menu for details). **Note:** The submission will be denied if any Investigators do not have current COI disclosures on file.
- The Additional Investigators must have a **current CITI course** on file (see the Amendment Handbook in the Help Menu for details)

See the Amendment Form Handbook in the help menu (orange and white question mark in the upper right corner) for further details on submitting these items.

3.4 If you are submitting a change in Research Staff note the following:

- The Research Staff must have a **current CITI course** on file (see the Amendment Handbook in the Help Menu for details)

4.0 Signature Instructions
READ THESE INSTRUCTIONS BEFORE PROCEEDING

4.1 To go to the signature routing pages:

Coordinators: Click "Save and Continue" and then "notify PI to signoff" (on the next page) to continue to the signature routing pages.
PIs: Click "Save and Continue" and then "Signoff and Submit" to continue to the signature routing pages

4.2 Signature Requirements

Only the signature of the PI is required on the **first** signature routing page. You may deselect other study staff from the routing list. If you are changing PI or making changes that prompt signatory requirements (click here for details), departmental or other signatories must be added on the **second** routing page.

4.3 If you have any additional comments that you would like to convey to the IRB staff, please enter them here:

DATA SAFETY MONITORING REPORT

Study: Genetics of Lung Disease (Exhaled Breath DNA Methylation in Lung Carcinogenesis) 2007-407

Date: 10/6/2017

Subject: Data safety monitoring

Committee members: Dr. Max O'Donnell (Columbia University Medical Center), Dr. Junchieh Tsay (NYU School of Medicine/ Medical Center), Dr. Timothy Harkin(Mount Sinai).

Principal investigator: Dr. Simon Spivack(Albert Einstein college of medicine)

Research coordinator: Dhruv Patel, Mohammad Aldabagh.

As a part of the study protocol, we organized the data safety monitoring meeting with Dr. O'Donnell, Dr. Tsay, and Dr. Harkins. Dr. Spivack gave a brief introduction of the study structure, data safety, accurate data of the patients enrollments and adverse events related to the procedures. Since October 2015 we have enrolled total 68 participants to the study which includes 16 surgical cases and 52 bronchoscopy cases. We have not reported any adverse event because of the procedures we use for sample collection. Our DSM committee seems satisfied with the data safety, the patient safety and ongoing patient enrollment. All questions of DSM committee members, were answered, there were no concerns on patient safety and data safety.