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DESIGN OF THE SUBPOPULATIONS AND INTERMEDIATE OUTCOMES IN COPD STUDY (SPIROMICS)

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Abstract

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SPIROMICS is a multi-center observational study of chronic obstructive pulmonary disease (COPD) designed to guide future development of therapies for COPD by 1) providing robust criteria for sub-classifying COPD participants into groups most likely to benefit from a given therapy during a clinical trial, thereby improving the chances of successful outcome; and 2) identifying biomarkers/phenotypes that can be used as intermediate outcomes to reliably predict clinical benefit during therapeutic trials, thus reducing costs. The goal is to enroll 3,200 participants in four strata: severe COPD, mild/moderate COPD, smokers without airflow obstruction and non-smoking controls. Participants undergo a baseline visit including morphometric measures, spirometry, six-minute walk, an inspiratory and expiratory chest CT, and a set of standardized questionnaires. Biospecimens, including plasma, serum, DNA, urine and induced sputum, are collected and stored. There are three annual follow-up examinations, with quarterly telephone calls to assess for exacerbations, hospitalizations and mortality. Bronchoscopy is being performed in a subset of participants and a subset of COPD patients will be assessed during exacerbations. Adjudication of exacerbations and mortality will be undertaken. SPIROMICS is designed so that sub-studies and ancillary studies testing additional hypotheses can be added.

Keywords

COPD Exacerbations; Emphysema; Imaging/CT MRI etc; COPD epidemiology

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic, usually progressive, lung disease characterized by incompletely reversible airflow obstruction. Both the airways (obstructive bronchiolitis/small airways disease) and the parenchyma (emphysema/parenchymal destruction) contribute to the airflow obstruction and ultimately dyspnea. Additional processes such as mucous hypersecretion (chronic bronchitis) and exacerbations contribute to the overall impact of the disease. COPD is the third leading cause of death in the US [1].

There are no proven medical therapies for COPD, other than supplemental oxygen and smoking cessation, that significantly reduce mortality [2]. No pharmacological treatments have been shown to modify meaningfully the long-term decline in lung function. Complicating the therapeutic scenario is the fact that the disease is highly heterogeneous. Obstructive bronchiolitis and emphysema are clinically distinct histological entities, but individual patients with COPD may have either or both. Moreover, each can occur in the absence of spirometrically defined COPD and likely result from a number of mechanistic pathways. The recognition of COPD as a systemic disease that affects extra-pulmonary systems, including cardiovascular, sleep and muscle function, further complicates disease classification. Because of clinical and pathological heterogeneity, individual patient subtypes may benefit from unique therapeutic regimens. Identifying meaningful subpopulations of COPD patients is a key goal of SPIROMICS. Additionally, the efficiency and cost of clinical trials could be improved considerably by validated intermediate endpoints.

OBJECTIVES OF SPIROMICS

SPIROMICS has two primary aims. Primary Aim 1 is to identify homogeneous subgroups of COPD patients for targeted enrollment in future therapeutic clinical trials. Primary Aim 2 is intermediate endpoint discovery and validation. SPIROMICS will endeavor to identify intermediate outcome measures that predict long-term clinical endpoints of morbidity. There are also three secondary aims, involving cohort building, developing a COPD controlled vocabulary, and supporting ancillary studies.

Further details of the aims and other aspects of the study are provided in the On-line Supplement.

STUDY DESIGN AND METHODS

SPIROMICS is a prospective cohort study that will enroll 3,200 participants into four strata (Non-smokers, Smokers without airflow obstruction, Mild/Moderate COPD, and Severe COPD) as shown in Table 1.

Participants may be enrolled in concurrent observational studies, excluding the COPD Gene Study [3], which will facilitate combined analyses between SPIROMICS and COPD Gene. Subjects enrolled in therapeutic clinical trials may enroll in SPIROMICS after the treatment is unmasked; those in SPIROMICS may be recruited into other interventional studies after SPIROMICS baseline values are obtained.

The Institutional Review Boards/Ethics Committees of all the cooperating institutions have approved the study protocols.

Inclusion and exclusion criteria

Participants must be 40–80 years of age at baseline, have a smoking history of ≥ 1 pack-year (Stratum 1) or ≥ 20 pack-years (Strata 2–4) and meet lung function criteria as specified in Table 1. Major exclusion criteria are non-COPD obstructive lung disease or a history of diseases or treatments likely to interfere with interpretation of study tests, BMI > 40 kg/m² at baseline, hypersensitivity to or intolerance of the bronchodilators used in study assessments and diagnosis of unstable cardiovascular disease. Lung surgery and metal in the chest that may affect the chest CT interpretation is also exclusionary. Supplementary Table 1 contains the complete list of exclusion criteria.

Baseline and follow-up assessments

There are baseline (Visit 1) and three annual in-person follow-up visits (Visits 2–4). Participants also receive quarterly follow-up calls to assess health status and determine if an exacerbation has occurred. Visits 1, 2 and 4, include anthropometry, seated blood pressure, spirometry, 6-minute walk test, biological specimen collection, and a series of questionnaires (Supplementary Table 2). Information is collected on medical history, respiratory exposures and current medications. Visit 3 omits specimen collection. Visits 1 and 2 include a thoracic CT scan at maximum inspiration and expiration.

Clinical outcomes, including hospitalizations and deaths, will be adjudicated centrally.

Imaging

Acquisition of state-of-the-art computed tomography (CT) images is a key component in SPIROMICS for detailed phenotype identification (Supplementary Table 3). Two CT scans are performed, one at total lung capacity (TLC), and one at residual volume. The CT protocol for the TLC scan is identical to that used in other NHLBI-sponsored studies including the Multi-ethnic Study of Atherosclerosis (MESA) Lung Study and the Severe Asthma Research Program (SARP), which will facilitate comparative papers across studies.

Biospecimen collection

Fasting blood and urine specimens are collected at Visits 1, 2 and 4. Approximately 70 ml of blood is collected per visit, including plasma, and serum. DNA will be extracted from blood collected at Visit 1 and RNA from PAX-Gene™ tubes collected at Visits 1 and 2. Urine is collected into aliquots with and without preservative. One EDTA plasma specimen is assessed locally for complete blood, differential and platelet count. All other samples are sent to the SPIROMICS biospecimen repository. Additional blood and urine samples are collected from participants in the sub-studies. Induced sputum samples are collected at the baseline visit. Sputum is being processed using the “whole sputum” method.

SUB-STUDIES AND ANCILLARY STUDIES

A sub-study is a component of the protocol funded by the SPIROMICS contract and performed on a subset or the entire cohort. An ancillary study is one that contributes new data to SPIROMICS but whose aims are distinct from the parent study. Ancillary studies are not funded as part of the parent study. However, they must be approved by SPIROMICS to assure that the use of SPIROMICS resources are scientifically and practically justified and that the study does not interfere with the primary goals of SPIROMICS.

Three key sub-studies are 1) the Repeatability and Replicate Sub-study, in which 100 participants will have the entire baseline clinic visit including the CT scanning repeated in order to quantify reliability and short-term within-person variability of study procedures and assay methods; 2) the Bronchoscopy Sub-study, in which 300 participants will undergo bronchoscopy with bronchoalveolar lavage, epithelial brushings and bronchial biopsies; and 3) the Exacerbation Sub-study, in which up to 400 participants will be followed prospectively and biological samples and clinical information will be collected at the time of an acute exacerbation.

STUDY ORGANIZATION

SPIROMICS has six core clinical centers, with sub-sites and satellite clinics, and several central agencies. These are the NHLBI Project Office, a Genomics and Informatics Center (which functions as the data and statistical coordinating center and includes the biospecimen core), a Radiology Center, a Pulmonary Function Test Reading Center, and a Sputum Reading Center. An Observational Studies Monitoring Board provides annual and ad hoc evaluations of the study with recommendations to the NHLBI. An External Scientific Board that is composed of representatives from the pharmaceutical industry and the Food and Drug Administration (FDA) serves in an advisory role.

DISCUSSION

The marked clinical and mechanistic heterogeneity that characterizes COPD confounds development of novel treatments. It is likely that mechanistically-based therapy will be effective only in selected subsets of the COPD population. SPIROMICS is designed to identify meaningful subsets of the COPD population appropriate for future mechanistically-based therapeutic interventions. Furthermore, the identification and validation of meaningful intermediate outcomes would facilitate development and testing of new treatments by enabling the design of more efficient clinical trials [4]. Although a number of such measures have been suggested, the validation of these measures is limited by the lack of data in a well-characterized, longitudinal COPD cohort.

Several other studies will complement SPIROMICS to help address these questions. ECLIPSE [5] utilized a three year observation period similar to SPIROMICS and shares similar goals. COPDGene [3] was originally designed to explore the genetics of COPD in a large cohort of subjects. Longitudinal data and collection of blood biomarkers are now in progress.

While the goals for SPIROMICS are ambitious, there are limitations. Even combined with other large studies like COPDGene and ECLIPSE, SPIROMICS will not be able to fully characterize COPD heterogeneity, its natural history or to fully validate biomarkers and other intermediate outcomes. These goals will undoubtedly require additional studies. SPIROMICS is committed to sharing protocols, instruments and data with other investigators. The availability of standardized methods and datasets will facilitate the development of other large cohorts and expedite their comparison with SPIROMICS and other studies.

Strengths of SPIROMICS include the large cohort with two types of controls, detailed characterization at baseline and longitudinally, and extensive follow-up, with central adjudication of clinical outcomes.

In summary, SPIROMICS is a prospective observational study of COPD subjects and controls. It will characterize individuals with clinical, physiologic, imaging, biochemical, cellular and histologic parameters. Samples will be collected by a variety of methods. A subset of participants will be assessed at the time of an exacerbation. The rich characterization of COPD subjects will permit definition of meaningful subsets of COPD patients. By assessing the relationship of clinical measures with longitudinal outcomes, SPIROMICS will advance validation of intermediate measures to be used in COPD. Finally, the availability of a well-characterized cohort of participants that can be used in specific ancillary studies should prove to be a long-term resource for furthering understanding of COPD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

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David Couper takes responsibility for the overall content as guarantor. The manuscript was written primarily by Drs. Couper, Rennard, and Han. It is based on the (unpublished) SPIROMICS protocol. Dr. LaVange, as PI of the Genomics and Informatics Center at the time, and Dr. Rennard as Chair of the Steering Committee, led development of the study protocol. All authors were involved in planning various aspects of the study and all authors reviewed the manuscript and provided feedback.

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Table 1

SPIROMICS Enrollment Strata

	Non-Smokers (Stratum 1)	Smokers (Stratum 2)	Mild/Moderate COPD (Stratum 3)	Severe COPD (Stratum 4)
Smoking Status	< 1 pack-year	> 20 pack-years	> 20 pack-years	> 20 pack-years
Bronchodilator Status for Assessing Lung Function	Pre-bronchodilator	Post-bronchodilator	Post-bronchodilator	Post-bronchodilator
FEV₁/FVC ratio criteria	FEV ₁ /FVC > 0.7	FEV ₁ /FVC > 0.7	FEV ₁ /FVC < 0.7	FEV ₁ /FVC < 0.7
Other Lung Function Criteria	FVC>LLN	FVC>LLN	FEV ₁ > 50% pred.	FEV ₁ < 50% pred.
Sample Size	N = 200 (6.25%)	N = 900 (28.1%)	N = 1500 (46.9%)	N = 600 (18.75%)

FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; LLN: lower limit of normal