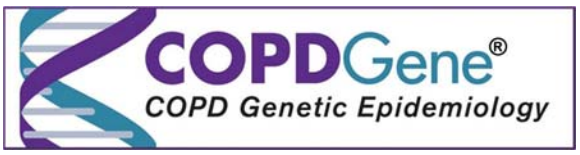


Version 5.0; June 19, 2009

STUDY PROTOCOL: GENETIC EPIDEMIOLOGY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPDGene®)

I. BACKGROUND AND SIGNIFICANCE

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of mortality in the United States (1). COPD is a heterogeneous syndrome, with varying contributions of emphysema and airway disease in each COPD subject. Genetic studies of complex diseases like COPD have the potential to provide insight into the pathophysiological mechanisms of COPD susceptibility and heterogeneity. A strong genetic basis for the susceptibility of smokers to develop COPD is suggested by: 1) Marked variability in the development of airflow obstruction among smokers (2); 2) Clear familial clustering of COPD and COPD-related phenotypes (3); and 3) Linkage of COPD-related phenotypes to specific genomic regions in families with severe, early-onset COPD (4). Case-control studies have been performed for many candidate genes in COPD, but the results have been inconsistent (5). Possible contributors to these inconsistent results include: 1) small sample sizes; 2) inadequate classification of distinct phenotypes (e.g., emphysema vs. airway disease); 3) widely varying criteria used for case definition and control selection in different studies; 4) failure to assess (and, if necessary, adjust) for population stratification; 5) testing a limited number of genetic variants in each candidate gene; 6) genotyping error; and 7) lack of correction for multiple statistical testing. Recent progress in single nucleotide polymorphism (SNP) genotyping allows for association studies on a genome-wide scale, rather than limiting analysis to recognized candidate genes or regions of linkage; however, the multiple statistical tests involved in genome-wide association (GWA) studies of thousands of SNPs raise challenges in separating true from false positive associations (6). In addition, genetic association studies within a single racial/ethnic group may not generalize to other populations. To address the multiple testing and generalizability problems of GWA studies, we propose to perform a comprehensive GWA study to identify genes influencing COPD in two major racial/ethnic groups (non-Hispanic Whites and African Americans). Our primary hypotheses are:

(1) Precise characterization of COPD subjects using computed tomography – as well as clinical and physiological measures assessed longitudinally – will provide insight that will enable the broad COPD syndrome to be decomposed into clinically significant subtypes.

(2) Genome-wide association studies will identify genetic determinants for COPD susceptibility that will provide insight into clinically relevant COPD subtypes.

(3) Distinct genetic determinants influence the development of emphysema and airway disease.

II. SPECIFIC AIMS

Specific Aim 1: Cohort Building
Identify and phenotype 4,500 COPD cases GOLD Stages 2 through 4, 4,500 smokers without COPD, 1,500 GOLD Stage 1 and GOLD U subjects, and 1,500 non-smokers without lung disease, from two racial/ethnic groups (non-Hispanic Whites and African Americans) for genetic, epidemiologic, and natural history studies.

Specific Aim 2: Genome-Wide Association Study
a. Phase 1. A genome-wide panel of SNPs will be tested for association with COPD in case-control samples from non-Hispanic Whites and African Americans.
b. Phase 2. Confirmation of SNPs yielding association signals in a second case-control population from the same racial/ethnic group to identify genomic regions for intensive investigation.
c. Phase 3. Mapping of fifty genomic regions yielding strong, confirmed association signals in a third case-control population from the same racial/ethnic group to identify susceptibility genes for COPD.
d. Phase 4. Fine mapping of candidate genes to identify susceptibility alleles and/or high risk haplotypes using multiple study designs and independent samples, including:
   - Entire set of case-control samples from both racial/ethnic groups
   - External validation using family-based association analysis in the Boston Early-Onset COPD Study and the International COPD Genetics Network

Specific Aim 3: Characterization of Subtypes of COPD
a. To further characterize the unique airway and parenchymal phenotypes of COPD by determining their associations with clinical, physiologic and functional indices.
b. Identify susceptibility genes for COPD subtypes, including CT-defined emphysema and CT-defined airway disease.

Specific Aim 4: Natural history of COPD and Risk Factors for Progression.
The cohort will be established for longitudinal follow-up with regular contact made to determine mortality, co morbid disease events and disease status based on clinical and/or chest CT evidence of progression.

III. SUBJECT SELECTION
We are recruiting 12,000 smoking and non-smoking subjects.

Subject Inclusion/Exclusion Criteria
A total of 12,000 non-Hispanic White and African-American subjects will be recruited. These subjects will be classified into four groups:
(1) Up to 4500 subjects with COPD GOLD Stages 2 through 4,
(2) Up to 4500 control subjects – current or former smokers without airflow limitation,
(3) Up to1500 subjects with minimal airflow limitation (COPD GOLD Stage 1) (7).
(4) Up to 1500 non-smoking control subjects, 500 African-American subjects and 1000 White subjects, with no smoking history and no airflow limitation

Subjects will be collected at 21 clinical centers in the United States.

General Inclusion and Exclusion Criteria for All Study Subjects
The following criteria will be required on ALL smoking and non-smoking study subjects:

Inclusion Criteria
Age 45-80 years
Non-Hispanic Whites and African Americans

Exclusion Criteria
Other concomitant respiratory disorder (such as, but not limited to, diffuse bronchiectasis, cystic fibrosis, or interstitial lung disease)
Lung surgery with removal of a lobe or more (including lung volume reduction and lung transplantation)
Lung cancer, known or suspected
Bronchoscopic lung volume reduction
Pregnancy or suspected pregnancy
Uncontrolled cancer, as defined as ongoing radiation therapy, ongoing chemotherapy, narcotics for pain control, or known metastatic disease
History of radiation therapy to the chest (other than radiation for breast cancer)
Use of antibiotics and/or systemic steroids (new prescription or increased dose) for a COPD exacerbation or any lung infection within the last month
Inability to use albuterol
First or second degree relative (parent, brother, sister, daughter, son, aunt, uncle, nephew, niece, half-sibling, grandparent, grandchild) of a subject enrolled in COPDGene®
Subjects who indicate they are in more than one racial category
Metal objects that may interfere with chest CT quantification including presence of a cardiac pacemaker, defibrillator, metal prosthetic heart valve, metal projectile or metal weapon fragment (bullet, shrapnel, shotgun shot) or metal shoulder prosthesis
Subjects unable to perform spirometry due to:
- chest or abdominal surgery in the past three months
- a heart attack in the last three months
- detached retina or eye surgery in the past three months
- hospitalization for any other heart problem in the past month

Participation in the ECLIPSE study
Inability to provide telephone contact number(s) and two additional contacts
Place of permanent residence of three months or more

Each of the four subjects groups contains specific criteria that define the distinct group. The criteria are relevant to the clinical and epidemiological categorization of the four study groups.

COPD Subjects:
Additional Inclusion Criteria
Smoking history of ≥ 10 pack-years
Diagnosis of COPD (post-bronchodilator $FEV_1/FVC < 0.70$) Stages 1, 2, 3 and 4 by GOLD criteria (7)
Additional Exclusion Criteria
Smoking history of < 10 pack years

The diagnosis of COPD includes airflow limitation on spirometry and history of risk factors (most commonly cigarette smoking) known to cause COPD. We will use NHANES predicted spirometry values obtained in the United States (8). There are no uniform criteria for the amount of cigarette smoking required for the diagnosis of COPD. We have chosen a threshold for cigarette consumption (10 pack-years) to ensure that all subjects have a substantial environmental stress to differentiate those who have an abnormal pulmonary response to cigarette smoke and those who do not have such a response. Review of medical records of patients with COPD frequently demonstrates a physician-listed diagnosis of asthma. These subjects will be included in the COPD groups if they have evidence of airflow limitation that is not fully reversible using the GOLD (Global Initiative on Obstructive Lung Disease) criteria. The interactions of asthma with COPD are common and complex. Elimination of asthma patients with fixed airflow limitation would inappropriately bias the findings of this study.

We will employ the FVC as the primary measure of lung volume since this will allow us to compare the study results to previous large-scale epidemiologic investigations. Normal values have been published and this maneuver is widely used. However, we will also collect the FEV_6, a more recently advocated index that may be easier for some patients to accomplish and reduce adverse effects of spirometry.

Subjects with known or suspected lung cancer will be excluded; if there are a substantial number of subjects with lung cancer in this study, then we may detect genes associated with lung cancer rather than with COPD. Subjects with a prior history of lung cancer, even if successfully resected and cured will be excluded. Subjects who may in the near future have a resection of a lesion suspected to be lung cancer will be excluded but may be included at a later time if the lesion proves not to be cancer and the resection removes less than one lobe of the lung.

Subjects with uncontrolled cancer of any type will be excluded because the cancer or cancer treatment may alter lung function and thus misclassify the respiratory status of the subject, and this cohort is being designed for long-term follow-up.

We will exclude patients with recent use of antibiotics and/or systemic steroids for a COPD exacerbation since such subjects may have an ongoing inflammatory pulmonary process related to an infection that will impair our ability to characterize and phenotype patients in their usual stable state. These patients can be re-screened 30 days after cessation of antibiotic or corticosteroid use.

GOLD Unclassified Subjects:

Additional Inclusion Criteria

Smoking history of $\geq$ 10 pack-years

Spirometry (Post-bronchodilator $FEV_1/FVC \geq 0.70$, $FEV_1 < 80\%$ predicted)

Additional Exclusion Criteria

Smoking history of < 10 pack years

Subjects that meet the required smoking history parameter but do not fall into either COPD or smoking control categories will be included as GOLD Unclassified subjects. These subjects will be grouped based on the occurrence of a normal spirometry accompanied by a presence of

reduced air flow (post-bronchodilator $FEV_1/FVC \geq 0.70$, low$FEV_1 < 80\%$). To date, we have found approximately 10-12% of our smoking subjects fall into this category. The inclusion of the Unclassified smoking group will provide additional and possibly novel information regarding the categorization, clinical presentation, and progression of COPD in smoking populations. Since this group is already present within the current subject pool, these subjects will be clarified as a distinct subject group.

Smokers without COPD

Additional Inclusion Criteria

History of cigarette smoking ≥ 10 pack-years

Post-bronchodilator $FEV_1/FVC \geq 0.70$ and $FEV_1 > 80\%$ predicted(9).

Additional Exclusion Criteria

Smoking history of < 10 pack years

Some potential subjects may have exclusionary criteria that only temporarily limit their enrollment in COPDGene®, such as recent use of antibiotics or corticosteroids. Such subjects with temporary exclusion may be re-screened and enrolled at a later time when these features are no longer exclusionary.

Subjects who have been given a diagnosis of COPD by a health care professional, but who have normal spirometry, will be enrolled as smoking control subjects. The diagnosis of COPD may have been incorrectly given to a patient without confirmation by spirometry. For this study, the diagnosis of COPD or lack thereof (based on the objective presence or absence of airflow limitation) will be determined by the post-bronchodilator spriometry performed as part of this study.

Sources of subjects will vary from center to center, but will likely include inpatient and outpatients at the centers, spouses and friends of subjects with COPD, patients in primary care practices, local patient support and educational groups, and local and national COPD voluntary organizations (such as COPD Foundation and American Lung Association).

Subjects should not primarily be recruited from sources that include a high prevalence of asthmatics such as asthma clinics or asthma patient groups. While subjects with asthma are not excluded in either control or COPD subjects in order to assure similar inclusion/exclusion criteria in both populations, the study is not designed as a study of the genetics of asthma. Thus subjects who have asthma as their primary respiratory disease should not be targeted for recruitment.

Although the primary focus of this project is COPD and COPD-related phenotypes, subjects will also be informed that this cohort may be used to study the genetic and environmental determinants of other smoking-related illnesses such as lung cancer and coronary artery disease and, with their permission on the consent form, other disorders that are not smoking-related.

Non-smoking Controls

Additional Inclusion Criteria

No smoking history as defined by less than 100 cigarettes smoked in a lifetime

No airflow limitation (Post-bronchodilator $FEV_1/FVC \geq 0.70$ $FEV_1 > 80\%$ predicted)

Additional Exclusion Criteria

Smoking history of more than 100 cigarettes smoked in a lifetime
Smoking history of more than 52 cigars smoked in a lifetime
Smoking history of more than 12 oz. of pipe tobacco smoked in a lifetime
No physician diagnosed history of respiratory disease

Subjects with no smoking history and no airflow limitation will be included as a reference population for comparison with those affected by smoking exposure. These subjects will also offer information on the processes involved in normal lung aging. Non-smoking control subjects are critical for supporting genetic and pathological findings within smoking and diseased subject groups by acting as a baseline for normal pulmonary physiology within a genetically mixed population.

IV. SUBJECT ENROLLMENT

This project will recruit a total of 12,000 subjects over five years using twenty-one clinical study centers. We anticipate that the recruitment will be completed early in the fifth year of the proposed study, allowing time for the genetic and epidemiologic analyses to occur by the end of the fifth year. Each Clinical Center will be expected to, on average, recruit approximately 160 subjects in each of the first four years meeting the program's defined recruitment goals for recruitment among both racial/ethnic classes, an approximately equal division of men and women, and with COPD subjects equally distributed among GOLD grades 1, 2, 3 and 4. The Executive Committee with the help of the Steering Committee will set and monitor goals for subject recruitment from each Clinical Center. The Administrative Core will have the right to modify recruitment goals between the centers to meet the overall goals of the project with respect to numbers of subjects recruited, minority subjects, or the balance of subjects in GOLD stages. The Administrative Core may incorporate additional qualified Clinical Centers if needed to meet recruitment goals.

Potentially eligible subjects who contact study staff or are referred by a health care professional may undergo screening either in person or by telephone to determine if they are likely to meet appropriate inclusion and exclusion criteria and to schedule the study visit to the Clinical Center. The study protocol will be discussed in detail during this screening encounter. A log will be maintained at each Clinical Center indicating the number of subjects who fail this initial screening. This screening log will be maintained at the Clinical Center and will not be transmitted to the Data Coordinating Center to assure confidentiality and protection of human subjects.

Before the study visit begins, written informed consent will be obtained by one of the study staff members. A physician investigator from the Clinical Center will be available to answer any questions regarding the informed consent process. Investigators may obtain consent from their own patients.

V. STUDY PROCEDURES

There will be one to two study visits for the majority of subjects depending on whether a separate visit is needed in order to schedule a Chest CT scan. In some cases, subjects may have a third visit to re-collect information that does not meet quality control criteria. For example, if spirometry does not meet quality control criteria as judged by the Pulmonary Function Core, the subject may be called to schedule an additional visit to repeat the test.

During their research study visit, the following procedures will be performed:

1. Informed consent will be obtained prior to any other study procedure.
2. Prior to any other evaluations, an Eligibility Questionnaire will be administered to determine if potential subjects meet inclusion/exclusion criteria. This questionnaire is located on the protected study web site and will provide a check on whether subjects meet inclusion and exclusion criteria.
3. Contact Information will be collected from the subject. Name, home address, phone number, cell phone, email address, date of birth and social security number will be collected from the subject. The purpose of this information is to maintain contact with the subjects up to four times a year for the purposes of longitudinal follow-up. Similar contact information (but not social security number) will be collected for two other individuals likely to know the subject's whereabouts, at least one of whom is a relative not living with the subject. The purpose of this information is to locate subjects who have moved to a different home and have a different address and/or phone number and ascertain vital status of the subject. All of this information will be maintained only at the local Clinical Center and will not be transmitted to the Data Coordinating Center.
4. Safety Assessment. A Safety Assessment questionnaire will be administered to subjects. They will be asked if they have a history of adverse events with the use of albuterol prior to administration of this inhaled bronchodilator. This safety assessment will also be used to ascertain potential cardiac disorders prior to albuterol administration and the walk test. If the questionnaire uncovers known or potential adverse effects of albuterol or potential cardiac disorders, a study physician will evaluate the subject to determine if it is safe to administer albuterol and perform a six-minute walk test.
5. Physical Assessment will be performed on all subjects: A limited assessment will be performed including height, weight, blood pressure, heart rate, and room air oxygen saturation by pulse oximetry with the subject seated at rest. In subjects using supplemental oxygen, the oxygen will be withheld and subjects will breathe room air for 10 minutes prior to recording oxygen saturation. If resting saturation falls below 82% or the subject becomes dyspneic prior to 10 minutes without oxygen, oxygen therapy will be restarted as a safety precaution. If heart rate is less than 50 or greater than 110 or if the blood pressure is greater than 170/100, a study physician will evaluate the subject to determine if it is safe to administer albuterol and perform a walk test.
6. Pre and post-bronchodilator spirometry will be performed on all subjects. The maneuvers are performed in a standardized manner. To obtain three acceptable measures, the technician may ask the subject to perform up to eight attempts. Spirometry is performed before and then repeated twenty to thirty minutes following the administration of two puffs (180 mcg) of albuterol from a metered dose inhaler with a spacer. Spirometry will be performed with the subject in the seated position with a nose clip in place. Inspiratory capacity will also be measured post-bronchodilator.

7. Standardized questionnaires will be completed by all subjects that meet entry criteria to assess respiratory history and symptoms, smoking history, family history, and other medical history. These questionnaires include a modified version of the American Thoracic Society/Division of Lung Diseases Respiratory Epidemiology Questionnaire (10) to assess respiratory symptoms and the St. George's Respiratory Questionnaire to assess health-related quality of life. Medications and oxygen use will also be recorded. Questionnaires can be administered by the method judged to be most convenient at each Clinical Center. Questionnaires may be interviewer-administered or self-completed on either a paper copy or directly on a computer pdf file. Completion of all questionnaires is expected to take between 45 and 90 minutes.
8. Blood is drawn from all subjects for DNA (genetic association studies) and serum and plasma (for measurement of other proteins potentially related to COPD and other diseases). A total volume of approximately 40 ml of blood will be drawn for this study. Blood samples will be stored at the Johns Hopkins COPDGene® Biological Repository.
9. Six-Minute Walk Test will be performed on all subjects to determine exercise capacity (11). This will be used to calculate the BODE score. Subjects will be asked questions to assure they do not have significant or occult heart disease prior to the test to assure subject safety.
10. Chest CT Scan will be performed to assess for emphysema and airway disease in all subjects. An inspiratory chest CT scan will be performed with a radiation dose of 200 mAs in order to provide thorough assessment of small airway wall thickness and emphysema. An expiratory chest CT scan will be performed of lower dose (50 mA) to assess for air trapping. If a clinical chest CT scan with an appropriate CT protocol and data storage has been performed within 6 months, that clinical CT scan may be used for this study with prior approval of the Imaging Committee that the scan algorithm used meets study criteria and can be analyzed appropriately. If a CT scan may not be scheduled on the same day as the study visit, the scan must be performed within 6 months after the visit. All COPD, Unclassified, and control subjects will be required to have a chest CT scan. If the chest CT scan is done on the same day as the post-bronchodilator spirometry, the scan should be scheduled as soon as possible after albuterol. The time and date of the last bronchodilator prior to the CT scan will be captured.
11. A urine pregnancy test will be performed on all premenopausal women prior to the chest CT scan.
12. Medical Record Review: In subjects with COPD, medical records will be reviewed when available with subject permission to obtain information within the last year of pulmonary function tests (including lung volumes and diffusing capacity) and oxygenation (arterial blood gases).
13. Longitudinal Follow-Up: Subjects will be contacted up to four times a year by telephone, mail, email, and/or newsletter to assess survival status and respiratory illnesses for up to 10 years.
14. Linking to other studies: Subjects with COPD will be asked if they are currently participating or have participated previously in other COPD NIH and non-NIH clinical trials such as the NHLBI COPD Clinical Research Network MACRO or LEUKO studies, NHLBI Long-Term Oxygen Therapy Trial (LOTT), National Lung Cancer Screening Trial (NLST), GlaxoSmithKline International COPD Genetics Network, Boston Early-Onset COPD Study, NHLBI Lung Tissue Research Consortium (LTRC), NHLBI Lung Health Study, and NHLBI SPIROMICS Study. Subjects will be asked if their clinical and genetic data can be linked to the results of these other studies and future investigations in order to investigate the

genetic associations between genotype data from this study with their outcomes in other trials.

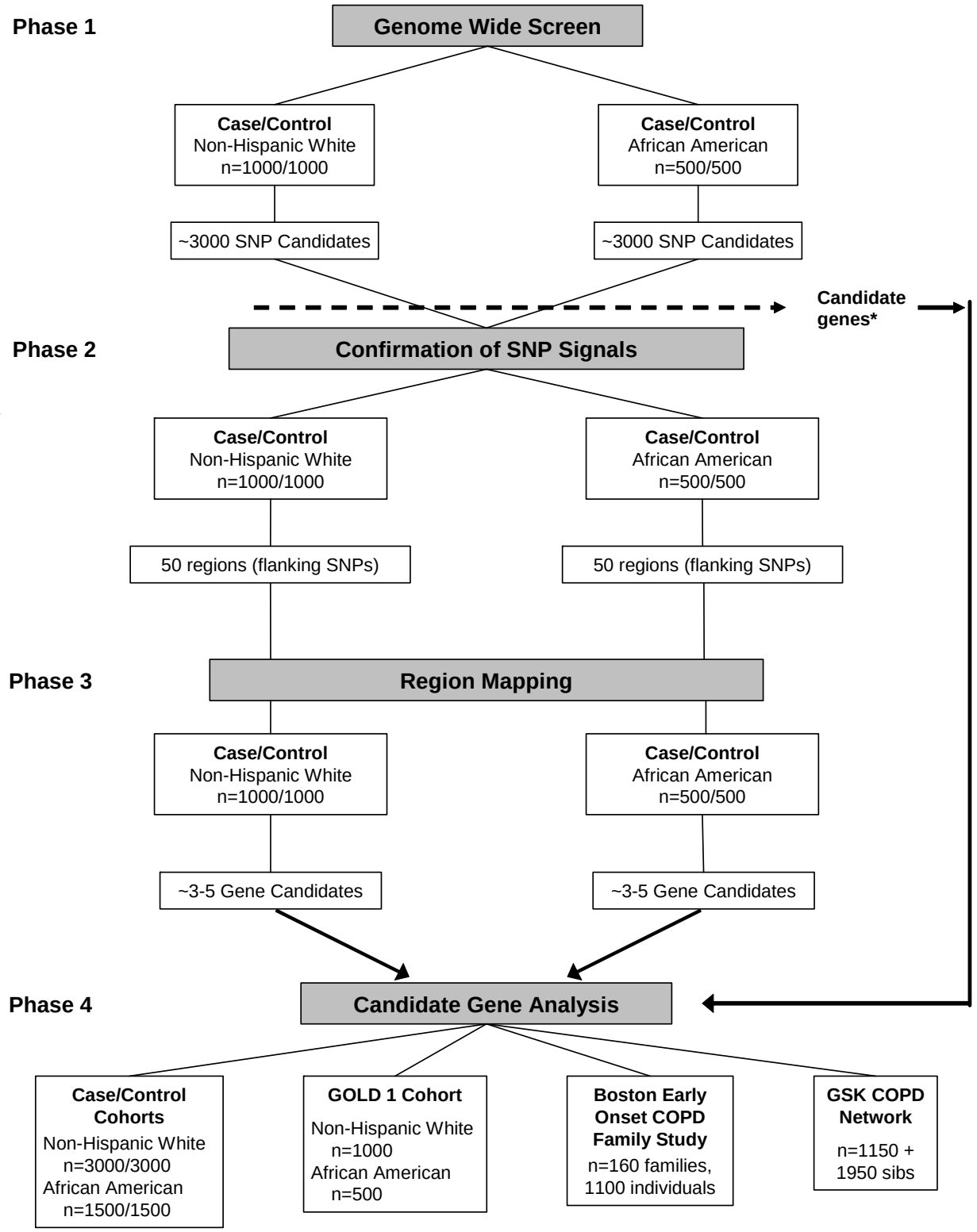
After the genotyping of candidate genes, including alpha 1-antitrypsin (AAT), is performed, subjects who elected to learn about abnormal AAT test results, when IRB approved, will receive them. These results may not be available for several years after the blood samples are obtained. For newly diagnosed PI ZZ subjects, the Principal Investigator of the Clinical Center will telephone those subjects first, then send a follow-up letter. Subjects with other abnormal PI types will be informed by mail. Participants will be informed that the AAT test results are based on research laboratory test results and should be repeated in a clinical laboratory. If subjects provide permission, these results will also be communicated to their physician.

The questionnaire and pulmonary function test results will be stored in a locked filing cabinet at each Clinical Center. Questionnaire and pulmonary function data, identified by study ID number only, will be transmitted to the Data Coordinating Center in Denver by secure internet connection with 132-bit encryption. Blood samples and CT scans will be transmitted to the appropriate Biorepository and Imaging Cores by overnight delivery service.

VI. BIOSTATISTICAL ANALYSIS

The genome-wide association analysis will be performed using a tiered replication strategy, as shown in this figure from the grant application:

Genome Wide Association of COPD: Study Design



Genome-wide association (GWA) analysis will be performed using a combination of novel and conventional analyses. Individual SNPs yielding genome-wide significant evidence of association to one or more of the 4 key phenotypes (COPD affection status, FEV_1, emphysema at -950 HU from CT scan, and airway wall thickness of 10 mm internal perimeter airways from CT scan) under Analysis Strategies 1 and 3 will be followed up with immediate candidate gene studies in Phase 4 ("Fast Track" SNP panel). Other promising SNPs associated with 1 or more of the 4 key phenotypes will be targeted for additional confirmation in Phase 2 studies (Analysis Strategy 2).

(1) Analysis Strategy 1: A novel analytical strategy that uses the same data set for both screening and testing individual markers will be used in both of the Phase 1 case-control samples. This strategy will identify robust and reproducible markers associated with COPD or its associated quantitative phenotypes. However, this strategy may not be able to identify all Disease Susceptibility Loci (DSLs), especially those of modest effect. We anticipate approximately 20 SNPs (5 for each of 4 phenotypes) will be identified for Fast Track analysis using this approach.

(2) Analysis Strategy 2: The first stage of a 2-stage analysis strategy will be applied to both of the Phase 1 samples using estimated effect size to identify 'important' SNPs. This will maximize statistical power to detect DSLs in subsequent Phase 2 studies, at the cost of potentially becoming more susceptible to heterogeneity among samples. Approximately 1500 SNPs for each of the 4 phenotypes will be included in Phase 2 confirmation studies; thus, 6000 SNPs in each racial/ethnic group will be identified for Phase 2 follow-up.

(3) Analysis Strategy 3: Joint analysis of p-values from both GWAs (non-Hispanic White case-control samples and African-American case-control samples) will be performed. This analysis will increase statistical power, but may be at greatest risk of spurious results from admixture/heterogeneity among samples. Adjustment for population stratification, which will be performed for each analytical strategy, will likely be most important for this approach. Approximately 20 SNPs will be identified for Fast Track analysis from this approach.

Power calculations were performed to assist in designing an efficient and effective multistage study. Simulation results based on 10,000 replicates of genotype and phenotype data were examined under a variety of model assumptions for alleles that are truly causal with odds ratio (OR) ranging from 1.30 to 1.75. For each simulated causal allele, the 2-stage design of Phases 1 and 2 was mimicked. In these simulations, we assumed 600,000 independent tests were performed corresponding to 600,000 separate SNP markers**.** Overall power is measured as the fraction of simulations in which the combined p-value of Phases 1 and 2 (based on Fisher's method) was below the threshold for genome-wide significance (5%/600,000). For GWAs in case-control designs, power calculations for the sample size of non-Hispanic Whites in this study (1000 non-Hispanic White COPD cases and 1000 controls) are shown in Table 1. For OR $\geq$1.5, this design will provide excellent statistical power.

Table 1 Statistical power to detect an effect of a disease susceptibility locus in a 600,000 SNP screen using 1000 cases and 1000 controls where the gene effect is small (allele effects OR=1.3-1.5).			
	Odds Ratio		
	1.30	**1.40**	**1.50**
Allele freq	Power	Power	Power
0.10	0.04	0.26	0.61
0.20	0.23	0.72	0.95
0.30	0.44	0.89	0.99
0.40	0.50	0.93	0.99

Table 2 Statistical power to detect an effect of a disease susceptibility locus in a 600,000 SNP GWA screen using 500 cases and 500 controls where the gene effect is moderate (OR=1.3-1.75)			
	Odds Ratio		
	1.30	**1.50**	**1.75**
Allele freq	Power	Power	Power
0.10	0.01	0.08	0.62
0.20	0.02	0.40	0.92
0.30	0.05	0.56	0.99
0.40	0.08	0.59	0.98

Table 2 shows the estimated statistical power for African Americans. There will be less statistical power in this group. These estimates of power are also based on 10,000 simulated replicates. Even though the smaller sample sizes for African Americans will provide less statistical power for the GWA of Phase 1, they do offer the immediate opportunity to test for consistency of marker effects on risk to COPD across racial/ethnic groups, and there will be adequate power to detect common alleles exerting substantial genetic effects (OR $\geq$ 1.75) in this minority group. Any marker that was significant in the non-Hispanic White group, and yielded estimated effect sizes of similar direction and magnitude (albeit of lesser significance) in the other racial/ethnic group, would be given higher priority. Thus, this study offers the opportunity to immediately test for consistency in evidence, and creates additional opportunities for more detailed follow-up studies when Phase 1 and Phase 2 samples are analyzed jointly.

VII. RISKS AND DISCOMFORTS

The only drug administered in this study is albuterol, as part of the pulmonary function testing. Two puffs of albuterol (180 mcg) are given via metered dose inhaler, with an Aerochamber spacer. After waiting 20 minutes, spirometry is performed. This is a one-time dose only. Albuterol is a commercially available, FDA-approved drug. The common side effects associated with albuterol are transient tachycardia, tremulousness, and nervousness.

There is a possible risk in questionnaire administration from inadvertent disclosure of medical history information. There is also a risk of loss of confidentiality. These potential risks are guarded against by maintaining completed questionnaires in a locked filing system in a locked room at the Clinical Centers, password-protected computers, and using secure transmission of information to the DCC. Pulmonary function and questionnaire data, identified by study ID number only, will be transferred by secure internet connection (with 132 bit encryption) to the Data Coordinating Center at National Jewish Medical and Research Center in Denver. Study personnel at Clinical Centers will be required to meet local requirements for training in protection of confidentiality.

Potential risks of blood drawing are hematoma at the skin site and minimal pain of venous puncture. Occasionally during or after pulmonary function testing, subjects may become

temporarily more short of breath. Subjects who are using oxygen may become short of breath when the oxygen is removed. However, this should rarely occur since oxygen will only be discontinued for 10 minutes and the oxygen saturation will be continuously monitored during this time.

Information about participation in a genetic study may influence insurance and/or employers regarding the health status of study participants. On the informed consent form, subjects will be informed that not sharing information about their participation in this study with others will minimize these risks. For newly diagnosed AAT Deficient subjects in this study, literature from the Alpha-1 Foundation regarding AAT Deficiency will be provided, and referral to a genetic counselor will be suggested.

Radiation exposure in the chest CT scan could theoretically increase the risk of cancer. Exposure of pregnant women to CT scan radiation could be harmful to the developing fetus. To minimize the likelihood of exposing pregnant women to CT scans, females of child-bearing potential will be asked if they are pregnant or have the possibility of being pregnant before the chest CT scan. CT scans will not be performed for women who state they are pregnant or that they may be pregnant; other pre-menopausal women will undergo urine pregnancy testing before a chest CT scan is performed. Chest CT scans could identify pulmonary nodules that may require follow-up outside of this study. Such pulmonary nodules could be curable lung cancers (a benefit) or scars/prior granulomas that could require additional radiation exposure or even surgery (a risk).

The maximum amount of radiation exposure during the chest CT scan is approximately 10 mSv. The radiation dose differs with body size; thinner subjects will have less than this amount of radiation. The average amount of background doses of radiation that the general population is exposed to in the United States is 3 mSv per year. Thus, the maximum amount of radiation subjects will receive is equivalent to about three years of normal background radiation.

There are no costs associated with participating in this study and subjects will not be paid for their participation. Participants will be compensated for their time and expenses for study visits in this study as follows. Participants will be compensated $75 for study visits for taking part in this research study if they complete breathing tests, questionnaires, 6-minute walk test, a chest CT scan, and donate blood.

This study is designed to be a national resource for scientific investigations. As such, medical information, genetic information and samples will be provided to other investigators, with appropriate safeguards. Other researchers interested in using such information for scientific investigations will be required to apply to the Executive Committee for permission to access the data for studies that have received local IRB approval and with requirements to maintain subject confidentiality. Subject identifying information will not be transmitted to other investigators.

VIII. POTENTIAL BENEFITS

There are no expected benefits to the study participants. Improved understanding of COPD may occur. As noted above, chest CT scans could identify pulmonary nodules or other abnormalities

that may require follow-up outside of this study. Some subjects may be informed that they potentially have alpha-1 antitrypsin deficiency.

IX. MONITORING AND QUALITY ASSURANCE

This is an observational cross-sectional investigation without a therapeutic intervention. It is expected that there will be deaths in both control and COPD subjects enrolled in this study that are not related to study procedures. It is expected that there will be hospitalizations from a variety of causes not related to study procedures including but not limited to newly discovered disorders, acute disorders requiring surgery, pre-existing conditions, and exacerbations of underlying COPD. Subjects may expire due to pre-existing or new diseases including cancer, cardiovascular conditions and COPD. These are anticipated events that are not related to this investigation. These events will not be prospectively collected as part of the current study and thus will not be reported to IRBs. There are no expected Serious Adverse Events in this study related to study procedures. At each Clinical Center, subjects will be observed for the development of tremulousness, and nervousness following bronchodilator medication. Unexpected Adverse Events related to study procedures will be reported to the IRB of the Clinical Center and to the Executive Committee. An Observational Safety and Monitoring Board will be appointed by the National Heart, Lung, and Blood Institute and will oversee this study.

Quality assurance of spirometry data will be insured by the Pulmonary Function Core in Utah, which will review de-identified spirometry data from each study participant. Quality assurance of CT scans will be analyzed by the Imaging Core in Denver. Questionnaires and other data will be quality controlled by the Data Coordinating Center in Denver.

X. REFERENCES

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