EXECUTIVE SUMMARY – COPDGene 2
Genetic Epidemiology of COPD

The COPDGene Project has been funded by the NHLBI for a second five years (2012-2017).

This is an NHLBI-funded multi-institutional observational study of past and current smokers to identify the genetic factors that control the development and progression of COPD and to facilitate development of specific therapies for the different subtypes of COPD. The first five-year phase of the COPDGene Project created a cohort of over 10,000 smokers who are at risk for or express one of the various stages of COPD (GOLD grades 1-4). This cohort was enrolled at 21 U.S. medical centers, and the subjects were phenotyped using inspiratory and expiratory HRCT. A genome-wide association study was done on the entire cohort and pilot whole exome sequencing was carried out.

The overall hypothesis underlying COPDGene is that extensive phenotypic and genetic data will enable creation of a new classification system for COPD, with distinct diagnostic, prognostic and therapeutic implications. The second five-year phase of COPDGene (2012-2017) is focusing on the following four goals:

1. Longitudinal Follow-up of the COPDGene Cohort to Find Determinants of COPD Progression
A five-year follow-up clinical visit of all available COPDGene subjects (approximately 8,000) is being done and includes repeat clinical evaluation, questionnaires, and inspiratory and expiratory chest CT scans.

2. Identification of Rare and Common Genetic Determinants of COPD
   a. We will genotype the Exome Chip in all COPDGene subjects and test for rare and common variant associations with baseline and longitudinal COPD-related phenotypes.
   b. We will perform whole genome sequencing of subjects with distinct imaging characteristics to identify rare and common genetic variants influencing COPD susceptibility, emphysema, and airway disease.

3. Create a New Classification System for COPD using Imaging, Clinical and Genetic Data
Using imaging, clinical, and genetic data, COPDGene is developing and validating a new classification system for COPD, which will dissect it into distinct pathophysiologic subtypes of this disease. Protein biomarker levels are being compared between COPD subtypes to identify biomarkers that associate with specific COPD subtypes.

This effort requires a combination of state-of-the-art genetic analysis (both rare and common variant methods) and state-of-the-art phenotyping (quantitative CT imaging, physiology, clinical
assessments and biomarker assessments) to define COPD subtypes. Both statistical and machine learning techniques are being used to integrate these data types to identify unique COPD subtypes.

4. Support Development of New COPD Therapeutics Targeted at Specific COPD Subtypes

The validation of specific COPD subtypes is expected to result in a paradigm shift in how this disease is approached and thereby enable the development of new subtype-specific therapeutics. In the future, we anticipate that the COPDGene cohort will be used to validate and execute clinical trials focused on the unique pathogenesis of specific COPD subtypes. This is expected to result in smaller and more effective clinical trials enabling the development of personalized therapy for subjects with different types of COPD. We will begin by monitoring outcomes of COPDGene subjects who are participating in clinical trials organized by the pharmaceutical industry or other entities—and this coordination will be enabled through COPDGene ancillary studies.

### Characteristics of the COPDGene Cohort

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### GOLD Classification of Smokers in the COPDGene Cohort

![GOLD Classification of Smokers in the COPDGene Cohort](image)
Data Sets Available on the COPDGene Cohort — Data being made available through dbGaP

Demographics: Age, race, gender, smoking history, educational level

Medical History: Co-morbid diseases, environmental exposures, respiratory symptoms, family history of COPD, chronic oxygen use, exacerbations, chronic medications

Function and Quality of Life: Six-minute walk distance, spirometry, St. George’s Respiratory Questionnaire, SF-36, Fagerstrom index for nicotine addiction

Imaging: Inspiratory and expiratory CT, quantification of emphysema, gas trapping and airway characteristics

Genetics: GWAS using Illumina Omni-Express chip; whole exome DNA sequencing and Exome Chip analysis on subset

Phenotyping the COPDGene Cohort Using Chest CT

Image-Based Biomarkers of COPD

Emphysema – severity, pattern, distribution
Quantitate percent of lung and of all lobes having density < -950 HU

Airway Disease – severity, type, distribution
Quantitate airway wall characteristics for third, fourth and fifth generation airways

Gas Trapping (percent of lung > -856 HU on expiratory scan)

Quantitative lung imaging is part of COPDGene. This is a 76-year old woman with FEV1 90% pred., FEV1/FVC ratio 0.61, segmental airway wall area percent 64%, emphysema 5%, and gas trapping 22%. The data were obtained automatically. The figure illustrates the level of airway resolution and the colored balls representing emphysematous air spaces color-coded by lobe.
Image-Based COPD Subtypes

Based on the previous quantitative image analysis and the newly funded visual image analysis of chest CT scans from the first phase of COPDGene, the following distinct image-based elements of COPD can be identified:

1. **Mild Centrilobular Emphysema (Mild CLE)**
   - Upper lung predominant

2. **Moderate/Severe Centrilobular Emphysema (CLE)**
   - Upper lung predominant
   - Lower lung predominant
   - Diffuse

3. **Panlobular Emphysema (PLE)**
   - Upper lung predominant
   - Lower lung predominant
   - Diffuse

4. **Paraseptal Emphysema (PSE)**

5. **Bulla**

6. **Large Airway Disease (LAD)**

7. **Bronchial Airway Disease (BAD)**

8. **Small Airway Disease (SAD)**
   - Obstructive
   - Inflammatory

9. **Pulmonary Vascular Disease (P/A ratio)**

10. **Interstitial Lung Abnormalities**

Genotyping the COPDGene Cohort

The entire cohort has been genotyped for SNPs on the Illumina Omni-Express platform. In Phase 2 of COPDGene, the entire cohort has been genotyped using the Illumina Exome Chip to assess rare and common coding variant associations with COPD-related phenotypes. At least 2000 COPDGene subjects, selected based on physiologic and imaging characteristics, will undergo whole genome sequencing.

Validation of findings will be done through collaborations with large COPD cohorts such as ECLIPSE, the International COPD Genetics Network, and the Boston Early Onset COPD Study. An International COPD Genetics Consortium has been established to facilitate combined genetic imaging and subtyping work across all major COPD cohorts worldwide.
Subtyping COPD – Development of a New Classification of COPD

The current spirometry-based classification systems for COPD severity (e.g. GOLD, ATS-ERS) do not address the inherent heterogeneity of COPD, but rather lump all COPD subjects together based only on the degree of airflow obstruction. A new COPD classification scheme is needed that recognizes the diversity of the disease and creates homogeneous subtypes sharing a common pathogenesis.

Integration of Clinical and Imaging Data to Create Unique Pathophysiologic COPD Subtypes: Using both statistical and machine learning methods, clinical characteristics such as airflow obstruction, exacerbations, rapid progression, chronic bronchitis, 6-minute walk distance, co-morbidities and quality of life assessments are being integrated with imaging data to identify COPD subtypes.

Biomarker Characterization: At the five-year follow-up visit (to occur 2013-2017), COPDGene will collect fresh-frozen plasma and serum samples. Biomarker panels will be tested for association with disease-related axes and COPD subtypes. Significant relationships of biomarker levels to the new COPD classifications would confirm the biological plausibility of the classification system and suggest future mechanistic studies.
Industry Advisory Committee

Academic / Industry Partnership
Help translate this program into clinical applications and new therapies personalized for specific subtypes of COPD. Assist in identifying and validating subtypes of COPD that determine risk for disease progression and response to therapy.

Industry Advisory Committee Roles
- Design and support of biomarker analyses
- Design and support of longitudinal follow-up of cohort between study visits
- Collaborate in CT image analyses [develop for FDA acceptable biomarker(s)]
- Design and extension of genetic analyses
- Identification of early, pre-symptomatic COPD in smokers
- Collaborate in COPD subtype analyses (subtypes for targeted therapeutic interventions)
- Propose clinical trials as COPDGene Ancillary Studies
- Support and participation in semi-annual investigator meetings
- Industry Advisory Committee Meetings

Partnerships

Public
COPD Foundation – John Walsh, President

Pharmaceutical
AstraZeneca, Boehringer-Ingelheim Pharmaceuticals, Novartis, GlaxoSmithKline, Pfizer, Sunovion
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COPDGene Publications

Selected Publications from a Total of More than 100 (2009-2014). See www.copdgene.org for full listing and links to articles.