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 study of past and current smokers to identify the genetic factors that control the development and progression 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) will focus 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) will be done and will include 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 will develop and validate a new classification system for COPD, which will dissect it into distinct pathophysiologic subtypes of this disease. Protein biomarker levels will be 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. 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.

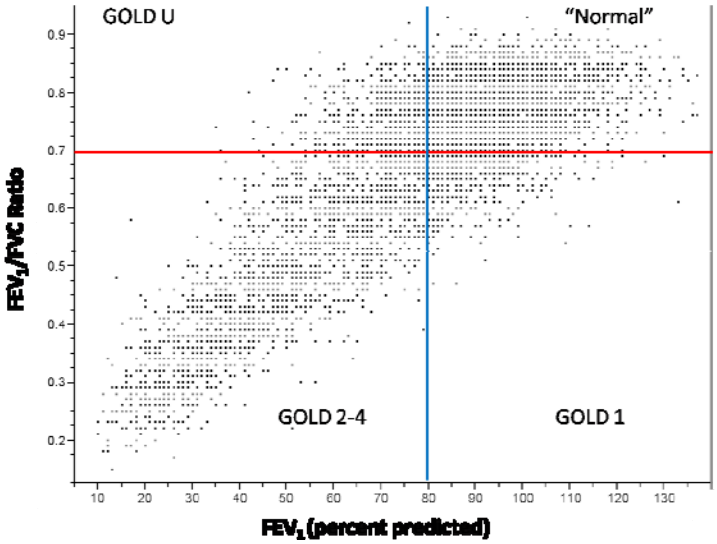
Characteristics of the COPDGene Cohort

Recruitment was completed in the spring of 2011. The current characteristics of the COPDGene cohort include:

Non-Hispanic White	Total Enrolled	Percent
Gender		
Male	3628	52%
Female	3302	48%
GOLD Status		
GOLD 0	2567	37%
GOLD 1/U	1385	20%
GOLD 2/3/4	2878	42%
Nonsmoker	100	1%
Totals	**6930**	**100%**

African American	Total Enrolled	Percent
Gender		
Male	1893	55%
Female	1541	45%
GOLD Status		
GOLD 0	1761	51%
GOLD 1/U	759	22%
GOLD 2/ 3/4	906	26%
Nonsmoker	8	0%
Totals	**3434**	**100%**

GOLD Classification of Smokers in the COPDGene Cohort



Data Sets Available from Initial Cohort Evaluation – 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

Imaging

Quantitative Image Analysis (QIL) is being done on two parallel platforms: VIDA and SLICER, with the following parameters being defined.

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)

Illustration of quantitative lung imaging being done by COPDGene. Image from Apollo System (VIDA) developed in conjunction with 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 with 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**

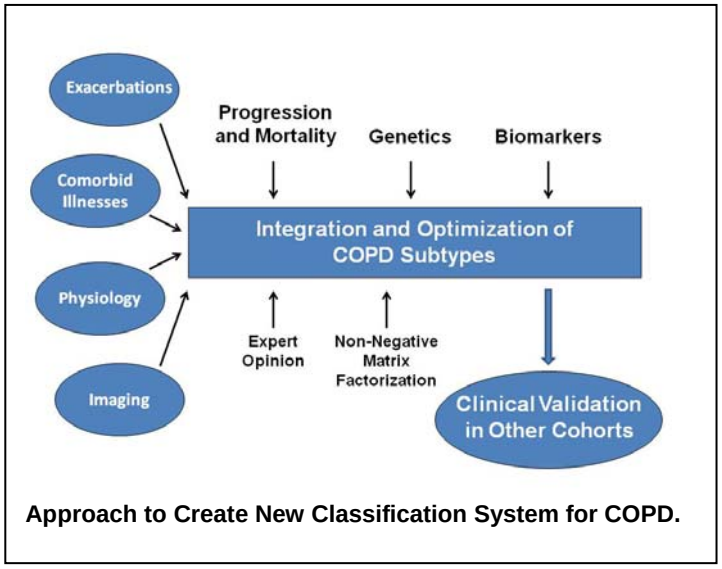
Genotyping the COPDGene Cohort

The entire cohort has been genotyped for SNPs on the Illumina Omni-Express platform. In Phase 2 of COPDGene, the entire cohort will be 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.



Approach to Create New Classification System for COPD.

The planned new COPD classification system will be initially based on clinical, physiological and radiological criteria, and will then use common and rare genetic variants as potential etiologies to refine this classification scheme.

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.

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)
- Clinical trials
- 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, Pfizer, Sunovion

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COPDGene Publications

Selected Publications from a Total of More than 50 (2009-2012). See www.copdgene.org for full listing and links to articles.

1. Regan EA *et al.* **Genetic epidemiology of COPD (COPDGene) study design**. COPD. 2010; 7:32-43.
2. Washko GR *et al.* **Identification of early interstitial lung disease in smokers from the COPDGene study.** Acad Radiol. 2010; 17:48-53.
3. Cho MH *et al.* **Variants in FAM13A are associated with chronic obstructive pulmonary disease**. Nat Genet. 2010; 42:200-2.
4. Diaz A *et al.* **Airway count and emphysema assessed by chest CT imaging predicts clinical outcome in smokers.** Chest. 2010; 138:880-7.
5. Washko GR *et al.* **Lung volumes and emphysema in smokers with interstitial lung abnormalities**. N Engl J Med. 2011; 364:897-906.
6. Budoff MJ *et al.* **Coronary artery and thoracic calcium on noncontrast thoracic CT scans: Comparison of ungated and gated examinations in patients from the COPDGene cohort**. J Cardiovasc Comput Tomogr. 2011; 5:113-8.
7. Kim DK *et al.* **Epidemiology, radiology, and genetics of nicotine dependence**. Respir Res. 2011; 12:9.
8. Kim DK *et al.* **Clinical and radiographic correlates of hypoxemia and oxygen therapy in the COPDGene study**. Respir Med. 2011; 105:1211-21.
9. Han MK *et al.* **Racial differences in quality of life in patients with COPD**. Chest. 2011; 140:1169-76.
10. Wan ES *et al.* **Clinical and radiographic predictors of GOLD-unclassified smokers in the COPDGene study.** Am J Respir Crit Care Med. 2011; 184:57-63.
11. Foreman MG *et al.* **Early-onset chronic obstructive pulmonary disease is associated with female sex, maternal factors, and African American race in the COPDGene study.** Am J Respir Crit Care Med. 2011; 184:414-420.
12. Han MK *et al.* **Chronic obstructive pulmonary disease exacerbations in the COPDGene Study: associated radiologic phenotypes.** Radiology. 2011; 261:274-82.
13. Castaldi PJ *et al.* **The association of genome-wide significant spirometric loci with COPD susceptibility.** Am J Respir Cell Mol Biol. 2011; 45:1147-53.
14. Rambod M *et al.* **Six minute walk distance predictors, including computed tomography measures, in the COPDGene cohort.** Chest. 2012; 141:867-75.
15. Cho MH *et al.* **A genome-wide association study of COPD identifies a susceptibility locus on chromosome 19q13.** Hum Mol Genet. 2012; 21:947-57.
16. Wells JM *et al.* **Pulmonary arterial enlargement and acute exacerbations of COPD.** N Engl J Med 2012; 367:913-21.
17. Galbán CJ *et al.* **Computed tomography-based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression.** Nat Med. 2012 Oct 7. (Epub ahead of print).