COPD Phenotypes and Personalized Medicine

Barry Make, MD
Professor of Medicine
Division of Pulmonary Sciences & Critical Care Medicine
National Jewish Health
Denver, Colorado
Learning Objectives

• List and discuss the most important COPD phenotypes
• Know how to assess COPD patients to determine their phenotype
• Outline and discuss management options individualized for important COPD phenotypes
Barry Make, MD

• Advisor for GlaxoSmithKline, Boehringer Ingelheim, Forest, Sunovion and Coviden
• Investigator for GlaxoSmithKline, Boehringer Ingelheim, Forest, AstraZeneca and Sunovion
• Speaker for GlaxoSmithKline and Forest

Disclosure Information

April, 2013
Are Phenotypes Important In Your COPD Patients?

YES

NO
• What is the most commonly accepted COPD “phenotypes”? 
What Is A “Phenotype”? 

• Observable characteristic or trait, such as morphology, development, biochemical or physiological properties or behavior 

• Appearance of an organism resulting from the interaction of the genotype and the environment 

• Outward, physical manifestation; observable structure, function, behavior, trait, characteristic 

1 Wikipedia  2 Dictionary.com  3 CUNY
COPD Phenotype Definition

“A single or combination of disease attributes that relate to clinically meaningful outcomes (symptoms, exacerbations, rate of disease progression or death).”

Have similar biologic or physiologic mechanisms
Defined by symptoms, radiography, physiology, biologic markers
[May] Respond differently to treatment

Han M, et al. AJRCCM 2010, 182:598
Rennard S, Vestbo J. Many Small COPDs. Chest 2008
Friedlander A, Bowler R. Phenotypes of COPD. COPD 2007
A common preventable and treatable disease, characterized by persistent airflow limitation, usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases [most commonly tobacco smoke], exacerbations and comorbidities contribute to the overall severity in individual patients.

Global Initiative For COPD. Diagnosis, Management and Prevention of COPD, Updated 2013. www.goldcopd.org
GOLD Phenotype 1

Airflow limitation
Presence or absence

GOLD Phenotype 1

Airflow limitation

Presence or absence

Is the spirometric FEV$_1$/FVC definition of COPD clear and precise?

? Fixed ratio < 0.70

? Lower limit of normal

GOLD Phenotype 2

Airflow limitation
Presence or absence
Degree of airflow limitation:
- GOLD Stage 1
- GOLD Stage 2
- GOLD Stage 3
- GOLD Stage 4

Do GOLD FEV₁ Stages Represent Phenotypes?

YES

NO
Do GOLD FEV₁ Stages Represent Phenotypes?

Different biologic mechanism?

Different clinical features?
- Symptoms
- COPD exacerbations
- Disease progression
- Mortality

Treatment response?
Correlation of Lung Function and Health Status Is Only Fair

SGRQ = St. George’s Respiratory Questionnaire

Poor Health

Good Health

SGRQ score

FEV₁ (%predicted)

Upper limit of normal

$r = -0.23$

$P < 0.0001$
Lung Function Correlates Poorly With Shortness of Breath

\[ y = 3.3 + 0.047 \times \quad r = 0.36 \]

Mahler D. COPD. 2004;1:165-172
More Frequent and More Severe Exacerbations as COPD Disease Severity Increased

Exacerbations were defined as events that led a care provider to prescribe antibiotics or corticosteroids (or both) or that led to hospitalization (severe exacerbations).

P<0.001 for both comparisons.

Is GOLD Stage 2 Chronic Obstructive Pulmonary Disease A Phenotype?
Factors Associated with Exacerbations in Individuals with GOLD Stage 2 Chronic Obstructive Pulmonary Disease

Brendan J. Carolan MD, Andre Williams Ph.D, Russell Bowler MD, Ph.D, Barry Make, MD

and the COPDGene Investigators.

ATS 2012
Confidential data from COPDGene® U01HL089897
<table>
<thead>
<tr>
<th>Variable</th>
<th>No AECOPD</th>
<th>AECOPD</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>n, %</td>
<td>1335 (70%)</td>
<td>584 (30%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.5</td>
<td>62.8</td>
<td></td>
</tr>
<tr>
<td>% Female</td>
<td>42</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>% African-American</td>
<td>26</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td><strong>28.5</strong></td>
<td><strong>29.8</strong></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking history (pk-yr)</td>
<td>50</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>% Current smokers</td>
<td>53</td>
<td>45</td>
<td></td>
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<tr>
<td>FEV1 (% predicted)</td>
<td>66</td>
<td>62</td>
<td>&lt;0.001</td>
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<tr>
<td>Walk distance (ft)</td>
<td>1331</td>
<td>1182</td>
<td>&lt;0.001</td>
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<tr>
<td>MMRC dyspnea score</td>
<td>1.4</td>
<td>2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SGRQ score (total)</td>
<td>27.9</td>
<td>45.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BODE index</td>
<td>1.3</td>
<td>2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Emphysema CT chest</td>
<td>8.2</td>
<td>9.9</td>
<td>&lt;0.009</td>
</tr>
<tr>
<td>% gas trapping CT chest</td>
<td>28.6</td>
<td>31.8</td>
<td>&lt;0.007</td>
</tr>
</tbody>
</table>
Factors Associated with Exacerbations

<table>
<thead>
<tr>
<th>Multiple Regression Analysis</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher MMRC Dyspnea Scores</td>
<td>0.02</td>
</tr>
<tr>
<td>Self-report of chest wheeze</td>
<td>0.05</td>
</tr>
<tr>
<td>Use of combined beta agonist/inhaled steroid (LABA/ICS)</td>
<td>0.01</td>
</tr>
<tr>
<td>African-American race</td>
<td>0.02</td>
</tr>
<tr>
<td>% Gas trapping (&lt;856 HU) on expiratory chest CT</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Weighting of Factors Associated with Exacerbations

<table>
<thead>
<tr>
<th>Random Forest Ranked Variables</th>
<th>Gini coefficient*</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Gas trapping on expiratory chest CT</td>
<td>23.5</td>
</tr>
<tr>
<td>Body mass index</td>
<td>19.0</td>
</tr>
<tr>
<td>Higher MMRC dyspnea score</td>
<td>12.0</td>
</tr>
<tr>
<td>Use of combined LABA/ICS</td>
<td>7.7</td>
</tr>
<tr>
<td>Report of chest wheeze</td>
<td>4.5</td>
</tr>
<tr>
<td>African-American race</td>
<td>3.8</td>
</tr>
<tr>
<td>Female gender</td>
<td>3.6</td>
</tr>
</tbody>
</table>

* Gini coefficient is a measure of the contribution of each variable to the association with exacerbations. Higher Gini values represent a greater contribution of that variable.
Response To Tiotropium (GOLD Stage 2)

Decramer M. Lancet. 2009
Do GOLD FEV₁ Stages Represent Phenotypes?

Different biologic mechanism?

Different clinical features?
- Symptoms
- COPD exacerbations
- Disease progression
- Mortality

Treatment response?
• Are there additional important COPD phenotypes?
• Are there additional important COPD phenotypes?
  - ? Frequent exacerbators
  - ? Gender
  - ? Chronic bronchitis
  - ? Chest CT scan
Exacerbations Become More Frequent and More Severe as COPD Airflow Limitation Increases

• Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Study - observational cohort of 2,138 patients followed for 3 years
  – Age 40-75 years, ≥10 pack-year smoking history, postbronchodilator FEV₁ <80% of predicted, FEV₁/FVC ratio <0.7

• Exacerbations: events that led a care provider to prescribe antibiotics or corticosteroids (or both) or that led to hospitalization (severe exacerbations)

Exacerbations Become More Frequent and More Severe as Airflow Limitation Increases

Results:

• Approximately 50% of patients had exacerbations in the first year of the study.

• Exacerbations were found to be more frequent and more severe as the severity of airflow limitation (GOLD Stage) increased.

• Single best predictor of exacerbations, across GOLD stages II through IV, was a history of exacerbations.

Frequent exacerbations = patients with $\geq 2$ exacerbations/year. Exacerbation requiring hospitalization = severe. Disease severity classified according to GOLD stages. $P<0.001$ for both comparisons.
Frequent Exacerbation Phenotype *

Frequent Exacerbation Phenotype *

Year 1

No exacerbations

1 exacerbation

≥ 2 exacerbations

Year 2

84 COPD patients from The London COPD Study; 70 patients completed the study (FEV$_1$ < 70% of predicted)
- Avg Age (yr): 67.8  Avg FEV$_1$: 40%

Measured daily PEF and respiratory symptoms for 1 year

Exacerbations diagnosed at an acute visit by the investigator or on review of diary cards
- Exacerbation: presence for ≥2 consecutive days of increase in any 2 “major” symptoms (dyspnea, sputum purulence, or sputum volume) or increase in 1 “major” and 1 “minor” symptom (nasal discharge, wheeze, sore throat, cough, or fever)

Patients completed St. George’s Respiratory Questionnaire (SGRQ) at their last clinic visit

Patients With More Frequent Exacerbations Had Worse Quality of Life


2Jones PW. Journal of COPD. 2005;2:75-79. SGRQ MCID in COPD is 4 units.

<table>
<thead>
<tr>
<th>Category</th>
<th>0-2 Exacerbations</th>
<th>3-8 Exacerbations</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>Mean Difference:</td>
<td>Mean Difference:</td>
<td>Mean Difference:</td>
</tr>
<tr>
<td></td>
<td>-15.1*</td>
<td>-21.9*</td>
<td>-12.2*</td>
</tr>
<tr>
<td>Symptoms</td>
<td>48.9</td>
<td>53.2</td>
<td>77.0</td>
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<tr>
<td>Activities</td>
<td>67.7</td>
<td>80.9</td>
<td>80.9</td>
</tr>
<tr>
<td>Impacts</td>
<td>36.3</td>
<td>50.4</td>
<td>50.4</td>
</tr>
</tbody>
</table>

*P ≤ 0.002

2Jones PW. Journal of COPD. 2005;2:75-79. SGRQ MCID in COPD is 4 units.
Relationship Between Exacerbations and Decline in Lung Function

- The London COPD Study (FEV₁ <70% of predicted)

- In diaries, 109 patients recorded daily PEF, increase in symptoms (above normal) over 4 years
  - Daily FEV₁ was recorded in subset of patients (n=32)

- Exacerbations were diagnosed based on diary cards or patients contacting the investigator
  - Exacerbation: presence for ≥2 consecutive days of increase in any 2 “major” symptoms (dyspnea, sputum purulence, or sputum volume) or increase in 1 “major” and 1 “minor” symptom (nasal discharge, wheeze, sore throat, cough, or fever)

Exacerbations Per Year

Results based on a secondary analysis of 32 patients who recorded daily FEV\textsubscript{1}.

Relationship Between Depression Scores and Exacerbations in COPD

- Prospective study of 169 COPD patients from The London COPD Study
  - Mean age: 70.9 years; Mean FEV$_1$: 47.0% of predicted
- Recorded daily respiratory symptoms on diary cards
- Depression score by the Centre for Epidemiologic Studies Depression (CES-D) Scale
  - CES-D score >16 indicates depressive symptoms
- COPD Exacerbations: two symptoms (one major) on 2 consecutive days or opinion of the attending clinician. Major symptoms were increased dyspnea, sputum volume, or sputum purulence; minor symptoms were increased cough, wheeze, sore throat, or coryzal symptoms

Patients With More Frequent Exacerbations Had Significantly Worse Depression Scores

Baseline Depression Scores by COPD Exacerbation Frequency

- 35% of infrequent exacerbators had a CES-D score >16
- 54% of frequent exacerbators had a CES-D score >16

* ≥ 3 COPD exacerbations in the preceding year
Arbitrary cut-off based on the median exacerbation frequency in the cohort

Increased Risk of All-Cause Mortality With Higher Number of Prior COPD Hospitalizations

Kaplan-Meier survival curve for time to death, stratified by the number of prior COPD hospitalizations (upper line 0, middle line 1, lower line 2 or more); p < 0.0001 by the log-rank test. McGhan R, et al. Chest. 2007;132:1748-1755.
Factors Associated With Increased Risk for Exacerbations

- Increased age\(^1,2\)
- Severity of airway obstruction (FEV1 impairment)\(^1,2\)
- Chronic bronchial mucous hypersecretion\(^2\)
- Longer duration of COPD\(^1\)
- Productive cough and wheeze\(^1\)
- Increased cough and sputum\(^3\)
- Antibiotic or systemic corticosteroid use in the past year\(^1\)
- Bacterial colonisation\(^4\)
- Comorbid conditions\(^5\) (e.g., cardiovascular disease)
- Poor health-related quality of life\(^6\)

Do Frequent Exacerbators Represent A COPD Phenotype?

Different biologic mechanism?
Different clinical features?
- Symptoms
- COPD exacerbations
- Disease progression
- Mortality

Treatment response?
Phenotypes?
Gender As A Phenotype?

More women die of COPD than men
Women may have lower lung function than men with the same cigarette exposure
Women may have more symptoms, depression, anxiety and poorer health status than men
Women may have more exacerbations
Women may have different lung anatomy

Mannino D. MMWR 2005
Celli B. AJRCCM 2011
Naberan K. Resp Med 2012
DiMarco Resp Med 2006
Ohar J. Prim RCJ 2011; 20:370
Gender and Chest CT Scan

2047 smokers in COPDGene
Compared men and women:

- Individual assessment of multiple airways: trachea to sub-segmental airways
- Measured
  - airway diameter,
  - airway lumen,
  - wall thickness,
  - wall area %

Kim Y et al. CHEST 2011
Measures Of Airway Wall Thickening

**Airway lumen:** \( L \)

**Airway diameter:** \( D \)

**Airway thickness:** \( D-L \)

**Airway wall %:**
\[
\frac{\text{wall area}}{\text{totarea al bronchial}} \times 100
\]

**AWT-Pi10:** square root of airway wall area of theoretical airway with internal perimeter of 10 mm
Airway Dimensions by Gender

- **Inner Diameter**
  - Males: 4
  - Females: 3

- **Lumen Area**
  - Males: 14
  - Females: 12

- **Wall Thickness**
  - Males: 2
  - Females: 1

- **Wall Area %**
  - Males: 65
  - Females: 63

All p < 0.001
Gender and Chest CT Scan

Women have thicker airways
higher wall area %
And smaller airways
lower airway internal diameter,
lower airway luminal area,
lower airway internal perimeter,
lower airway wall thickness

Kim Y et al. CHEST 2011
Gender and Chest CT Scan

Gender differences in airway dimensions may be associated with differential effects of cigarette smoking and COPD in men and women

Kim Y et al. CHEST 2011
Early Onset COPD

Gender Distribution by Age Groups
FEV\textsubscript{1} < 50% Predicted

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-49</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>50-54</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>55-59</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>60-64</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>65-69</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>70-74</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>75-80</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>
Early Onset COPD

Less Emphysema in EOCOPD
17% vs 23% (p<0.001)

Less Gas Trapping in EOCOPD
48% vs 56% (p<0.001)

Foreman M. Am J Resp Crit Care Med 2011
# Early Onset COPD Univariate Analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex (47)</td>
<td>2.6 (1.5–4.5)</td>
<td>0.0006</td>
</tr>
<tr>
<td>AA race (16)</td>
<td>4.4 (2.4–8.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pack-years of smoking</td>
<td>0.97 (0.96–0.98)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Maternal smoking (49)</td>
<td>2.9 (1.7–5.1)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Maternal COPD (14)</td>
<td>2.2 (1.1–4.5)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Foreman M. Am J Resp Crit Care Me,d 2011
Early Onset COPD Multivariate Analysis

<table>
<thead>
<tr>
<th>Characteristic (%)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex (47)</td>
<td>3.1 (1.1–8.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>AA race (16)</td>
<td>7.5 (2.3–24)</td>
<td>0.00007</td>
</tr>
<tr>
<td>Pack-years of smoking</td>
<td>0.98 (0.96–1.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Maternal smoking (49)</td>
<td>1.7 (0.6–4.7)</td>
<td>0.3</td>
</tr>
<tr>
<td>Maternal COPD (14)</td>
<td>4.7 (1.3–17)</td>
<td>0.02</td>
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</tbody>
</table>
Does Gender Represent A Phenotype?

Different biologic mechanism?
- Emphysema, airway disease

Different clinical features?
- Disease expression/progression
- AECOPD
- Symptoms
- Mortality

Treatment response?
Classic Representations of Patients with COPD

Emphysema

Chronic Bronchitis
COPD Phenotypes 2013: Chronic Bronchitis

1061 COPD GOLD Stage 2-4 subjects

Chronic bronchitis: cough and sputum for $\geq 3$ months a year for $\geq 2$ consecutive years (ATS respiratory questionnaire)

290 with chronic bronchitis (CB+) and 771 without chronic bronchitis (CB-)

Kim V et al. CHEST 2011
Impact of Chronic Bronchitis

MMRC Dyspnea (2, 3)

SGRQ Health Status (37, 50)

BODE Index

Kim V et al. CHEST 2011
AECOPD Frequency In Chronic Bronchitis

Kim V et al. CHEST 2011

AECOPD per year

CB+ 1.21

CB- 0.63

p < 0.027
Percentage of COPD Subjects With Severe AECOPD (hospitalization)

Kim V et al. CHEST 2011

% With Severe AECOPD

CB+ 26.6%

CB- 20%

p < 0.024
Chronic bronchitis subjects:
  Younger
  Smoked more
  More current smokers
  More wheezing and nocturnal awakenings
  Thicker airways – airway wall %
  More exacerbations; more severe AECOPD

Kim V et al. CHEST 2011
Does Chronic Bronchitis Represent A Phenotype?

Different biologic mechanism?
Different clinical features?
  ─ Mortality
  ─ AECOPD
  ─ Disease progression
  ─ Symptoms

Treatment response?
Chest CT Scan As A Phenotype?
GOLD Stage 2 COPD – FEV₁ 60% Predicted

Patient 1:
Marked Panlobular Emphysema - ULP

Patient 2:
Minimal Emphysema
Are Chest CT phenotypes associated with AECOPD?

- Emphysema
- Airway Disease
Chest CT Scan As A Phenotype?

- **COPD: Airway Predominant**
  - Small Airway Disease
    - Expiratory Air Trapping
    - Centrilobular opacities
    - Nodules / ground glass attenuation
  - Bronchial Wall Thickening
  - Other Large Airway Abnormalities
    - Bronchiectasis
    - Bronchial Out-pouchings
    - Saber Tooth Trachea
    - Tracheobronchomalacia
Annual Number of COPD Exacerbations

<table>
<thead>
<tr>
<th></th>
<th>Emph</th>
<th>Airway</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>29%</td>
<td>51%</td>
</tr>
<tr>
<td>BMI</td>
<td>22.7</td>
<td>30.7</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9.7%</td>
<td>19.5%</td>
</tr>
<tr>
<td>BODE</td>
<td>5.1</td>
<td>3.0</td>
</tr>
<tr>
<td>CV disease</td>
<td>9.5%</td>
<td>12.1%</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>28.0%</td>
<td>7.8%</td>
</tr>
</tbody>
</table>

Han M et al. Radiology 2011
Both bronchial wall thickness and emphysema are independently associated with exacerbation frequency in the prior year. Effect persists with correction for FEV1, age, gender, current smoking status.

1.7 fold AECOPD increase per 1 mm increase in airway thickness (not airway wall %)

1.18 fold AECOPD increase per 5% increase in emphysema >35%

Han M et al. Radiology 2011
### Table 2. Factors Independently Associated with Exacerbations at Enrollment and Follow-up.*

<table>
<thead>
<tr>
<th>Time Period and Factor</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History of severe exacerbations at enrollment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁, per percentage-point decrease</td>
<td>1.02 (1.01–1.03)</td>
<td>0.001</td>
</tr>
<tr>
<td>SGRQ, per 1-point increase</td>
<td>1.03 (1.02–1.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, per 1-year increase</td>
<td>0.97 (0.95–0.99)</td>
<td>0.002</td>
</tr>
<tr>
<td>PA:A ratio &gt;1</td>
<td>4.78 (3.43–6.65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Severe exacerbations during longitudinal follow-up</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbation in previous yr</td>
<td>2.01 (1.61–2.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV₁, per percentage-point decrease</td>
<td>1.02 (1.01–1.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SGRQ, per 1-point increase</td>
<td>1.02 (1.01–1.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GERD</td>
<td>1.22 (0.98–1.52)</td>
<td>0.08</td>
</tr>
<tr>
<td>Age, per 1-yr increase</td>
<td>0.99 (0.99–1.01)</td>
<td>0.74</td>
</tr>
<tr>
<td>PA:A ratio &gt;1</td>
<td>3.44 (2.78–4.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>All exacerbations during longitudinal follow-up</strong></td>
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</tr>
<tr>
<td>Exacerbation in previous yr</td>
<td>2.49 (2.09–2.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV₁, per percentage-point decrease</td>
<td>1.02 (1.01–1.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SGRQ, per 1-point increase</td>
<td>1.01 (1.01–1.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GERD</td>
<td>1.75 (1.47–2.08)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*NEJM 2012; 367:913*
Green – centrilobular (55%)

Orange – subpleura (19%)

Both (20%)

ILD – 6% (12)

Washko G et al. NEJM 2011; 364:897
Interstitial abnormalities:
- Less emphysema (-3%)
- Lower TLC by CT scan (-0.444 L)
- Greater smoking history

Compared to those w/o ILD:
- Less spirometric COPD (0.53 OR)
- Restrictive defect (<80% pred TLC by CT scan) (-2.3 OR)

Washko G et al. NEJM 2011; 364:897
Personalized medicine is treating:
• The *right* patient
• With the *right* treatment / medication
• At the *right* time in the course of the disease
• To achieve the *right* outcome
What is Personalized Medicine For COP?

Tailoring of medical treatment to each individual patient.
Employ specific preventative and therapeutic interventions on those who will benefit, sparing expense and side effects for those who will not.
Classify individuals into subpopulations that differ in their susceptibility to COPD or their response to a specific treatment.

Adapted from: President’s Council of Advisors on Science and Technology, September 2008
**Personalized Medicine in COPD**

Perform careful clinical assessment in each patient

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia</td>
<td>Supplemental oxygen</td>
</tr>
<tr>
<td>Emphysema</td>
<td>LVRS, AECOPD reduction</td>
</tr>
<tr>
<td>Chronic bronchitis, AECOPD, severe COPD</td>
<td>AECOPD reduction, targeted Rx</td>
</tr>
<tr>
<td>GOLD Category</td>
<td>Symptom reduction, AECOPD reduction</td>
</tr>
</tbody>
</table>
### Personalized Medicine in COPD

Perform careful clinical assessment in each patient

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<thead>
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<th>Phenotype</th>
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<tbody>
<tr>
<td>GOLD Stage 2</td>
<td>AECOPD reduction</td>
</tr>
<tr>
<td>Gender – AECOPD, mortality, symptoms</td>
<td>AECOPD reduction</td>
</tr>
<tr>
<td>Chronic bronchitis – AECOPD, symptoms</td>
<td>AECOPD reduction, targeted Rx</td>
</tr>
<tr>
<td>Emphysema</td>
<td>AECOPD reduction</td>
</tr>
<tr>
<td>Chest CT scan – AECOPD</td>
<td>AECOPD reduction</td>
</tr>
<tr>
<td>Others</td>
<td>?</td>
</tr>
</tbody>
</table>
Personalized Treatment in COPD

Environmental level
- Diet
- Smoking
- Pollution
- Infections
- Allergens
- Activity
- Temperature

Clinical level
- COPD
- Metab Syn.
- Osteoporosis
- Myopathy
- Cancer
- CVD
- Oxidative stress
- Acquired immunity
- Innate immunity
- Repair
- Ageing
- Bioenergetics
- GWAS
- Epigenetics
- miRNA
- miDNA
- ncRNA
- Pharmacogenomics

Biological level

Genetic level

Life-style
- Modifiable factors

Clinical phenotypes
- Integrated care
- Personalized medicine
- Guidelines network

Intermediate phenotypes
- Diagnostic biomarkers
- Therapeutic targets

Genetic markers
- Risk assessment

Agusti and Vestbo, AJRCCM, 2011
COPD Phenotypes

- FEV₁ is a traditional phenotype that does not fully explain COPD heterogeneity
- Women are different than men
- Clinical chronic bronchitis and emphysema are traditional phenotypes that have clinical importance
- Emphysema and airway disease subtypes may be classified by chest CT scan
- COPD exacerbations are more frequent in CT defined groups
COPD is a constellation of disorders differentially affecting the airways, lung parenchyma and vasculature with different biologic mechanisms. The differentiation of disorders is established by chest CT scan along with clinical features. COPD phenotypes have distinct genetic and biologic markers. Some of these disorders share the common feature of airflow limitation.