# Defining Phenotypes in COPD

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## Presenter Disclosures

**MeiLan K. Han**

<table>
<thead>
<tr>
<th>Consulting</th>
<th>Novartis</th>
<th>Bohringer Ingelheim</th>
<th>Grants</th>
<th>NHLBI</th>
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<td>NHLBI/FDA</td>
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<tr>
<th>Lecture Fees</th>
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<th>Grifols</th>
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<th>UpToDate</th>
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<td></td>
<td>Pfizer</td>
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<td>Continuing Education</td>
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</table>
What is COPD?

- Chronic obstructive pulmonary disease (COPD): a preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.


“Old” staging system for COPD

<table>
<thead>
<tr>
<th>GOLD Stage</th>
<th>I Mild</th>
<th>II Moderate</th>
<th>III Severe</th>
<th>IV Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ (%)</td>
<td>FEV₁ &gt;80%</td>
<td>FEV₁ 50-80%</td>
<td>FEV₁ 30-50%</td>
<td>FEV₁ &lt; 30%</td>
</tr>
<tr>
<td>Active reduction of risk factors: influenza vaccine</td>
<td>Add short-acting bronchodilators when needed</td>
<td>Add regular Rx with ≥1 long-acting bronchodilator when needed</td>
<td>Add rehabilitation</td>
<td>Add inhaled corticosteroids (ICS) if repeated exacerbations</td>
</tr>
<tr>
<td>Consider surgery</td>
<td></td>
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</tbody>
</table>

* If chronic respiratory failure.

“New” Staging System for COPD

Sub-Phenotypes of COPD

- Systemic Inflammation
- Peripheral Muscle
- Chronic Bronchitis
- Emphysema
- Airway Reactivity
- Small Airway Disease
- Emphysema Distribution
- Vascular Disease
- Interlobar Collaterals
What is a phenotype?

A phenotype is an organism's observable characteristics or traits such as its morphology, development, biochemical or physiological properties, that result from expression of an organism’s genes, influence of environmental factors and interactions between the two.
What is a phenotype?

Pink Puffers and Blue Bloaters

Does it Matter?
Phenotypes: A New Definition

Clinical Commentary

Chronic Obstructive Pulmonary Disease Phenotypes
The Future of COPD

“A single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression or death).”

Phenotype is defined by symptoms, radiology, physiology, biomarkers

Ultimately we would hope that phenotypes would have similar biologic or physiologic mechanisms

Han, et al. AJRCCM 2010;182:598.

Ideal Phenotyping Construct:
Paths to Phenotype Development

Han, et al. AJRCCM 2010;182:598.
**Phenotype vs Endotype**

Endotype: “Subtype of a condition, defined by a distinct functional or pathobiological mechanism. This is distinct from a phenotype, which is an observable characteristic or trait of a disease without any implication of a mechanism. It is envisaged that patients with a specific endotype present themselves within phenotypic clusters of diseases.”


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**Long-term Mortality in NETT**

NETT Research Group NEJM 2003;348(10):2059
Rationale for Roflumilast to Treat COPD

Adenylate cyclase

ATP → 3', 5'-cAMP (active)

Proteins

PDE-4

Roflumilast / Roflumilast N-oxide

ATP → ADP

Proteins

5'-AMP (inactive)

↓ Inflammation

- Inhibit the inflammatory mediators most relevant to COPD and associated exacerbations
- Affect cellular function in neutrophils, eosinophils, monocytes, and lymphocytes

ADP=adenosine diphosphate; AMP=adenosine monophosphate; ATP=adenosine triphosphate; PKA=protein kinase; Th1=type 1 T helper cell; Th2=type 2 T helper cell.


Evolution of Roflumilast Program
Identification of Target COPD Population

Early Phase III Studies M2-111, M2-112 Subanalyses

Confirmatory Pivotal Studies M2-124, M2-125

Hypothesis Generation

Treatment of COPD Associated With Chronic Bronchitis in Patients at Risk of Exacerbations
M2-111 / M2-112
Rate Ratio in Moderate or Severe COPD Exacerbations Favors Roflumilast

<table>
<thead>
<tr>
<th>Study</th>
<th>Favors roflumilast</th>
<th>Favors placebo</th>
<th>Reduction in Exacerbation Rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M2-111</td>
<td></td>
<td></td>
<td>-14.0</td>
</tr>
<tr>
<td>M2-112</td>
<td></td>
<td></td>
<td>-15.2</td>
</tr>
<tr>
<td>M2-111+M2-112</td>
<td></td>
<td></td>
<td>-14.3</td>
</tr>
<tr>
<td>Conc. ICS</td>
<td></td>
<td></td>
<td>-18.8</td>
</tr>
<tr>
<td>Bronchitis</td>
<td></td>
<td></td>
<td>-26.2</td>
</tr>
<tr>
<td>Emphysema</td>
<td></td>
<td></td>
<td>-1.1</td>
</tr>
</tbody>
</table>

Rate Ratio

M2-124 / M2-125
Key Inclusion Criteria

Severe to very severe COPD

- **Chronic bronchitis**
  - *Chronic productive cough for 3 months in each of the prior 2 years*

- **Exacerbation history (within 1 year prior to study)**
  - *At least 1 documented COPD exacerbation requiring systemic corticosteroids, hospitalization, or both*

- Age >40 years

- FEV₁/FVC ratio (post-bronchodilator) ≤70%

- FEV₁ (post-bronchodilator) ≤50% of predicted

- Current or former smoker with a smoking history of at least 20 pack-years

Roflumilast approved for COPD

FDA approves new drug to treat chronic obstructive pulmonary disease

Editor’s note: Deltorex has been approved as the trade name for roflumilast.
Phenotyping in Asthma vs COPD

**In Asthma:** molecular and cellular pathways of inflammation
- Eosinophilic/Th2 high inflammation

**In COPD:** tissue and organ level information
- Airway vs emphysema predominant disease
- Imaging

Interleukin-13 and asthma

Barnes, *Nat Rev Drug Discovery* 2004
The gene expression profile of epithelial brushings from asthmatic subjects

Healthy (n = 28)  Asthma (n = 42)

- Periostin
- CLCA1
- SerpinB2

Epithelial cell expression of these three genes is regulated by IL-13.

Woodruff et al. *PNAS* 2007

Clustering by expression levels of peristin, CLCA1 and serpinB2 in epithelial brushings identifies two groups of subjects with asthma

Woodruff et al. *AJRCCM* 2009
Serum periostin as predictor of response to lebrikizumab

Corren et al. NEJM 2011

Lebrikizumab Treatment in Adults with Asthma
Jonathan Corren, M.D., Robert F. Lemanske, Jr., M.D., Nicola A. Hansania, M.D., Phillip E. Kerenblat, M.D., Mendad V. Parsy, M.D., Ph.D., Joseph R. Arron, M.D., Ph.D., Jeffrey M. Harris, M.D., Ph.D., Helleen Scheerens, Ph.D., Lawren C. Wu, Ph.D., Zheng Su, Ph.D., Sofia Mirovtska, Ph.D., Mark D. Eisner, M.D., M.P.H., Sean P. Bohem, M.D., Ph.D., and John G. Matthews, M.B., B.S., Ph.D.

Corren et al. NEJM 2011 Sep 22;365(12):1088-98
Where do we go from here?

In vivo Measures of Disease

Parenchymal Disease       Airway Disease

Phenotypes
Ideal Phenotyping Construct: Paths to Phenotype Development

- Validation of Molecular Marker or Determination of Therapeutic Response in Target Population
- Development of Therapy
- Clinical Phenotype Defined by Similar Outcomes
- Symptomatic, Physiologic, and/or Radiologic Characterization of Phenotype
- Biologic or Molecular Characterization of Phenotype

Han, et al. AJRCCM 2010;182:598.

- 21-center, $35 million NHLBI initiative
- 10,500 subjects, cross-sectional
- To perform whole genome genotyping phenotyping correlation
  - State-of-the art HRCT
  - Physiologic assessment
  - Symptom/health status assessment
Phenotypic/clinical parameters and biological markers will enable COPD patients to be divided into homogeneous subgroups.

The same, or a different subgroup, of phenotypic/clinical and biological markers can be used as intermediate outcomes for use as clinical trial endpoints.

Assessments

- **Physiology**
  - Lung function testing
  - BMI, body composition

- **Imaging**
  - Serial CT scans

- **Biospecimens**
  - Blood, sputum, urine
  - Bronchoscopy

- **Patient reported outcomes**

- **Exacerbations**
  - EXACT-PRO
  - Unscheduled visit
  - Biospecimens
KOLD Cohort

- Designed to develop a systematic diagnostic model and integrative prognostic factor for obstructive lung disease.
- COPD & Asthma patients
- Recruited at 11 hospitals in South Korea 2005-2012
- Inspiratory / Expiratory CT data (n=307)
  - More than ½ of cases have f/u CT data of 3 or 6 years.

CT Assessment of Disease

Emphysema percent was quantified from HRCT using a threshold of ≤ -950 HU

Airway analysis examined in the 3rd generation (segmental) airway of each lobe.

Haswegawa, et al. AJRCCM 2006;173
Mortality by Phenotype

- Cohort of 947 ever-smokers (49% with COPD)
- 6-8 years of mortality data
- Significantly shorter survival for medium (3-10%) and high (>10%) LAA groups
- Pi10 did not predict mortality

Johannessen, et al. AJRCCM 2013 (in press)

Symptoms vs BODE

Exacerbation Frequency Increases With Disease Severity

Exacerbation was defined as an increase in dyspnea, sputum volume, and/or sputum purulence.


1.8 fold change in exacerbation frequency / 1% increase (p=0.004)

Disease Phenotypes

“Emphysema Predominant”

“Airway Disease Predominant”
**Pink Puffers and Blue Bloaters**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Emphysema Predominant</th>
<th>Airway Disease Predominant</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>96</td>
<td>174</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>65.31 (7.38)</td>
<td>63.72 (9.06)</td>
<td>0.12</td>
</tr>
<tr>
<td>Pack Years</td>
<td>55.30 (23.54)</td>
<td>53.36 (42.92)</td>
<td>0.57</td>
</tr>
<tr>
<td>Annual exacerbation rate</td>
<td>1.13 (1.35)</td>
<td>0.80 (1.37)</td>
<td>0.06</td>
</tr>
<tr>
<td>FEV₁ %</td>
<td>28.55 (12.17)</td>
<td>51.87 (21.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SGRQ score</td>
<td>49.75 (16.01)</td>
<td>40.72 (19.59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyspnea score (mMRC)</td>
<td>2.91 (1.07)</td>
<td>2.24 (1.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BODE</td>
<td>5.21 (1.74)</td>
<td>2.98 (2.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>9.3 (29.2)</td>
<td>12.1 (32.7)</td>
<td>0.35</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>9.3 (29.3)</td>
<td>19.5 (39.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Osteoporosis (%)</td>
<td>28.0 (45.2)</td>
<td>7.8 (26.4)</td>
<td>0.001</td>
</tr>
</tbody>
</table>


**How do we make the transition from phenotypes to endotypes?**
Implications of Emphysema Subtypes

- **Panlobular Emphysema**
- **Paraseptal Emphysema**
- **Centrilobular Emphysema**

Histologic Implications of Emphysema Subtypes

- 67 subjects undergoing lung resection
  - 27 smokers with centrilobular emphysema
  - 24 smokers with panlobular emphysema
  - 8 with no emphysema
- CLE was associated with mast cell increase in airway smooth muscle and airway hyper-reactivity as defined by methacholine challenge.

279 Patients with COPD & CT

Rapid decliners, slow decliners and sustainers identified (25th, 25-75th and 75th percentile)

- Emphysema severity but not FEV1 showed significant difference among the groups
- Multiple logistic regression demonstrated that rapid decliners were independently associated with emphysema severity.
- The “sustainers” displayed less emphysema and higher levels of circulating eosinophils.

Nishimura, et al. AJRCCM 2012; 185:44-52

**Biomarkers and Change in Lung Density**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Effect on Baseline Perc 15</th>
<th>P-value</th>
<th>Effect on Annual Change (g/l/yr)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>Coefficient</td>
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<tr>
<td>SPD</td>
<td>2.18</td>
<td>&lt;0.001</td>
<td>-0.23</td>
<td>0.004</td>
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<tr>
<td>sRAGE</td>
<td>3.87</td>
<td>&lt;0.001</td>
<td>0.24</td>
<td>0.001</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>-0.33</td>
<td>0.51</td>
<td>0.18</td>
<td>0.019</td>
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<tr>
<td>IL-6</td>
<td>-0.29</td>
<td>0.55</td>
<td>0.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-8</td>
<td>0.68</td>
<td>0.12</td>
<td>0.14</td>
<td>0.07</td>
</tr>
<tr>
<td>TNF-alpha</td>
<td>0.23</td>
<td>0.60</td>
<td>0.03</td>
<td>0.61</td>
</tr>
<tr>
<td>CRP</td>
<td>0.13</td>
<td>0.80</td>
<td>-0.21</td>
<td>0.012</td>
</tr>
<tr>
<td>CC-16</td>
<td>-0.84</td>
<td>0.09</td>
<td>-0.11</td>
<td>0.15</td>
</tr>
<tr>
<td>CCL-18</td>
<td>-1.56</td>
<td>0.001</td>
<td>0.012</td>
<td>0.13</td>
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Genetic Implications of Emphysema Subtypes

- 107 COPD subjects from the KOLD cohort
- Correlation between COPD phenotype and ADRB2 genotype
  - ADRB2 may be associated with bronchodilator responsiveness

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Arg/Arg</th>
<th>Arg/Gly</th>
<th>Gly/Gly</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumen area (mm^2)</td>
<td>11.1 ± 2.9</td>
<td>10.7 ± 2.6</td>
<td>9.5 ± 3.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Lumen diameter (mm)</td>
<td>3.63 ± 0.48</td>
<td>3.58 ± 0.46</td>
<td>3.34 ± 0.55</td>
<td>0.02</td>
</tr>
<tr>
<td>Airway thickness (mm)</td>
<td>1.23 ± 0.12</td>
<td>1.21 ± 0.12</td>
<td>1.24 ± 0.10</td>
<td>0.59</td>
</tr>
<tr>
<td>Wall area (mm^2)</td>
<td>17.8 ± 5.4</td>
<td>17.7 ± 5.2</td>
<td>16.4 ± 6.0</td>
<td>0.22</td>
</tr>
<tr>
<td>Wall area (%)</td>
<td>63.6 ± 4.2</td>
<td>63.7 ± 4.2</td>
<td>66.4 ± 5.4</td>
<td>0.02</td>
</tr>
</tbody>
</table>


Conclusions

- COPD is a systemic and heterogeneous disease
- Careful phenotyping including clinical, physiologic, radiologic and biologic assessments will be required for understanding the inflammatory mechanism behind COPD and developing targeted therapies
- Phenotype development in COPD will be an iterative, longitudinal process
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