Personalized Medicine in COPD Treatment

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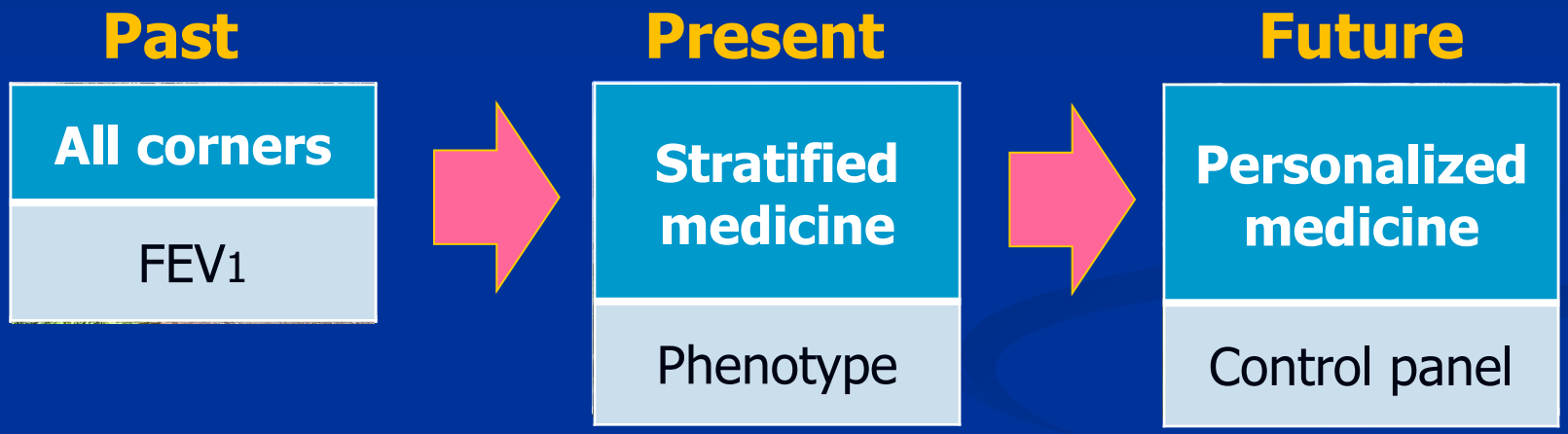
Personalized Medicine in COPD Treatment



COPD Stone Age: FEV_1-centric view

COPD Renaissance: Complexity, phenotypes and stratified medicine

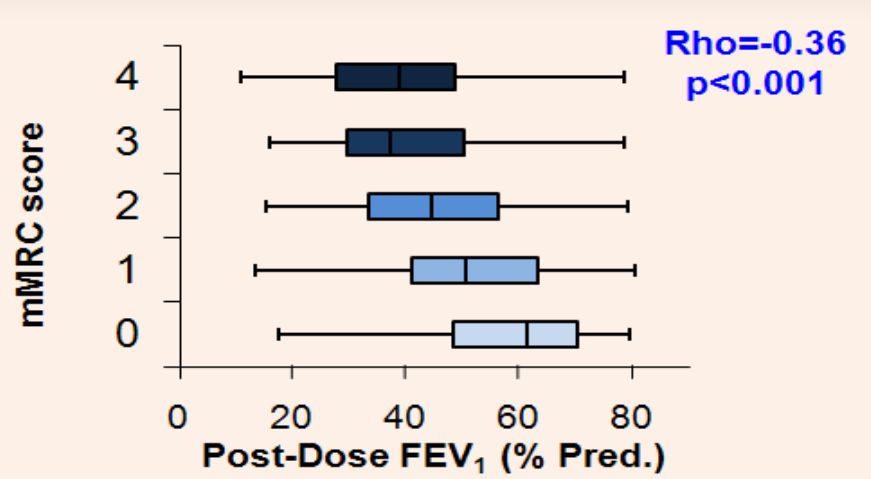
COPD Future: Personalized Medicine

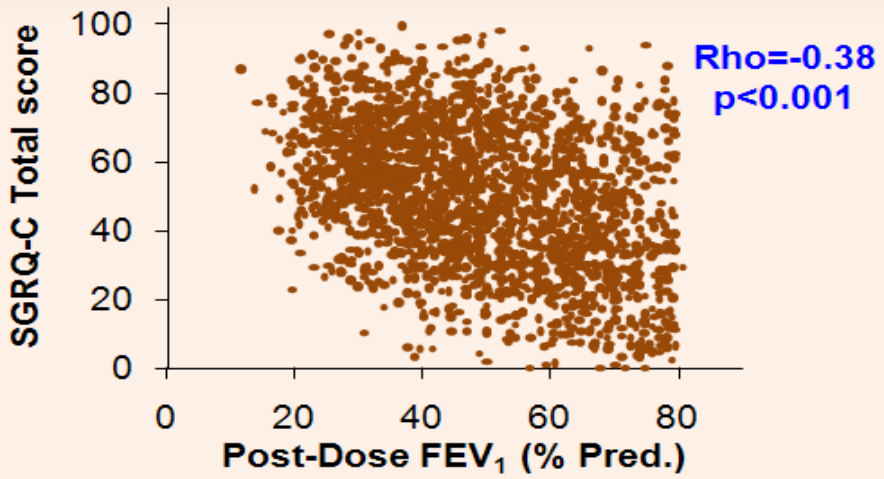
COPD Stone Age: FEV_1-centric view

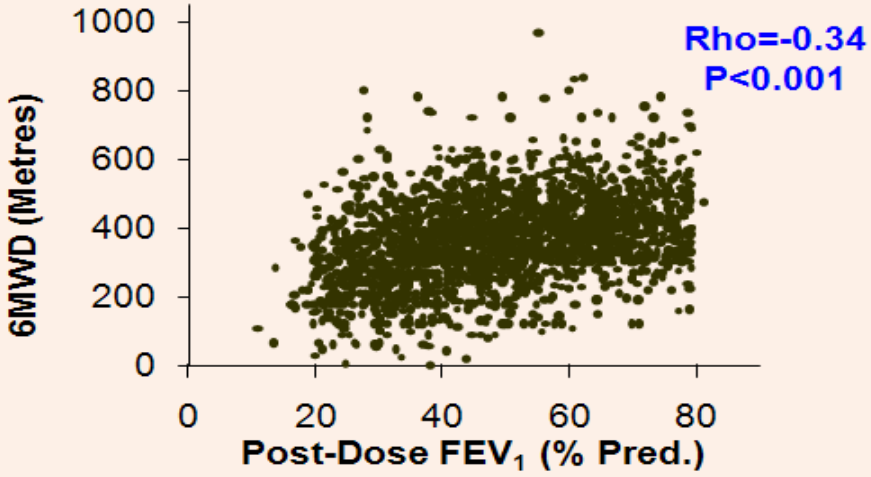
- 15-20 years ago
  : self-inflicted disease
  : persuading quit smoking
  : use short-acting bronchodilator, theophylline

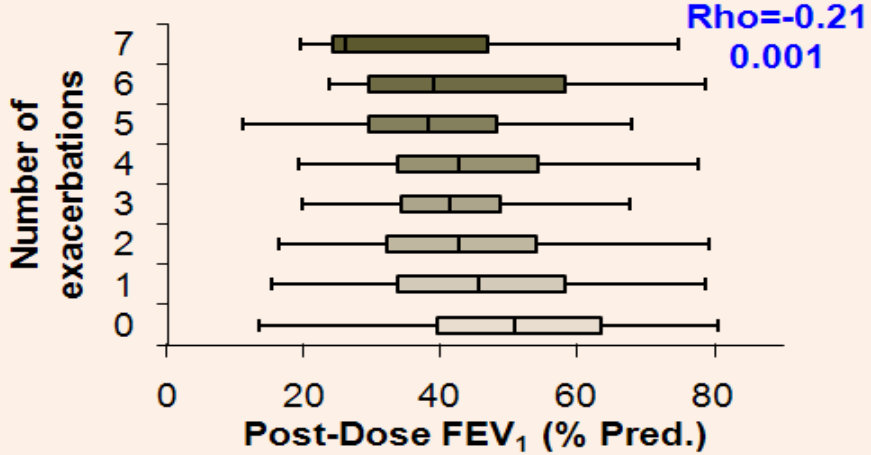
- Landscape began to change when the 2001 first GOLD document and first revision in 2006
  : persistent airflow limitation that is usually progressive
  : diagnosis, assessment, and therapy has been guided primarily by the degree of airflow limitation (FEV_1)

ECLIPSE showed Weak Correlation between Disease Outcome Parameters and FEV_1



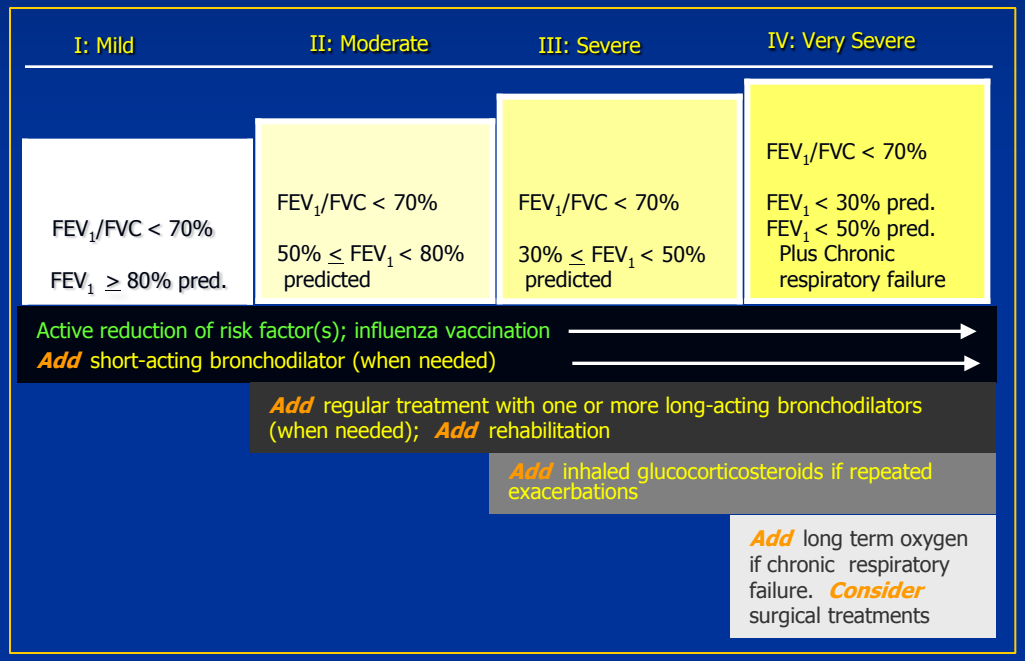




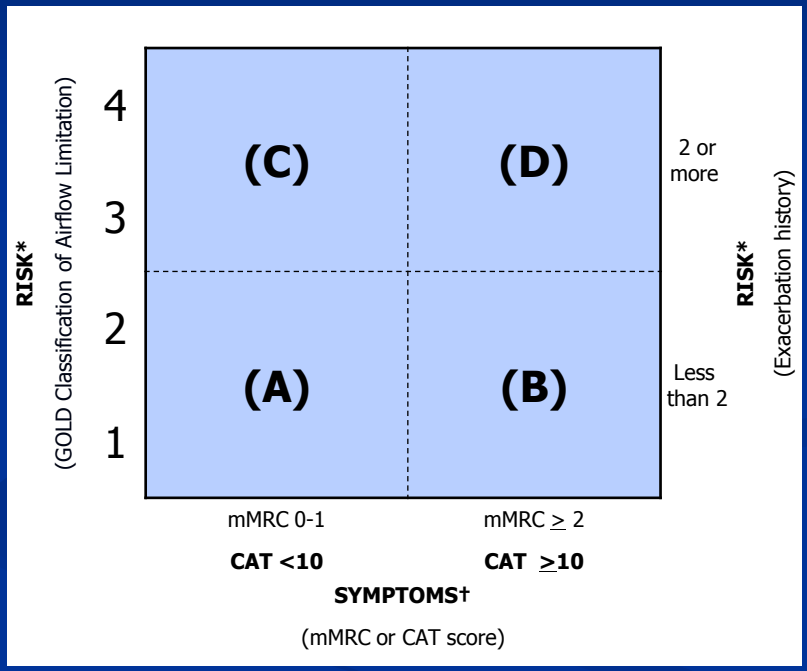


Agusti et al. Resp Res 2010; 11: 121

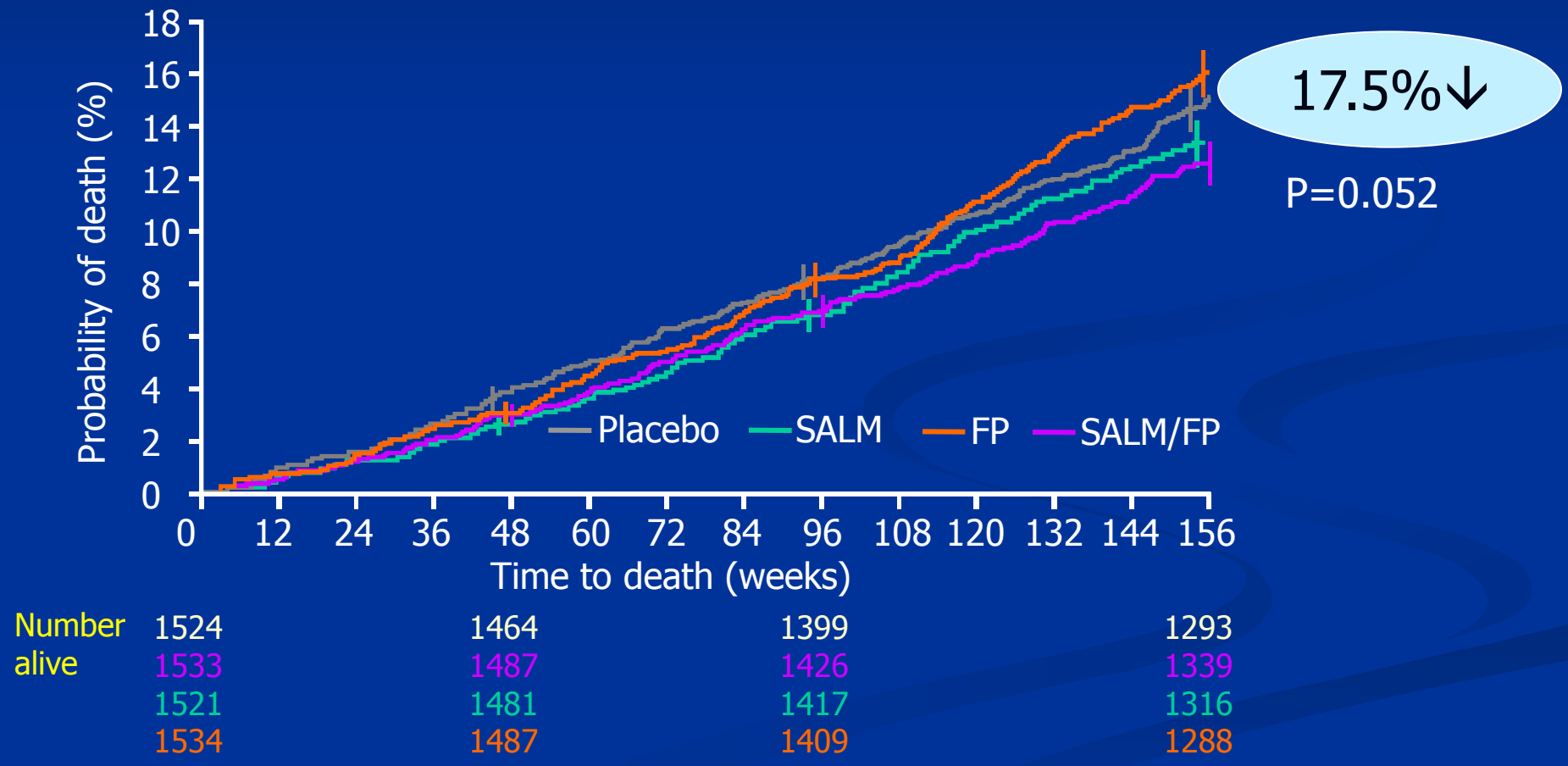
2006


I: Mild
II: Moderate
III: Severe
IV: Very Severe
FEV1/FVC < 70%
FEV1 ≥ 80% pred.
FEV1/FVC < 70%
50% ≤ FEV1 < 80% predicted
FEV1/FVC < 70%
30% ≤ FEV1 < 50% predicted
FEV1/FVC < 70%
FEV1 < 30% pred.
FEV1 < 50% pred.
Plus Chronic respiratory failure
Active reduction of risk factor(s); influenza vaccination
Add short-acting bronchodilator (when needed)
Add regular treatment with one or more long-acting bronchodilators (when needed); Add rehabilitation
Add inhaled glucocorticosteroids if repeated exacerbations
Add long term oxygen if chronic respiratory failure. Consider surgical treatments

2011

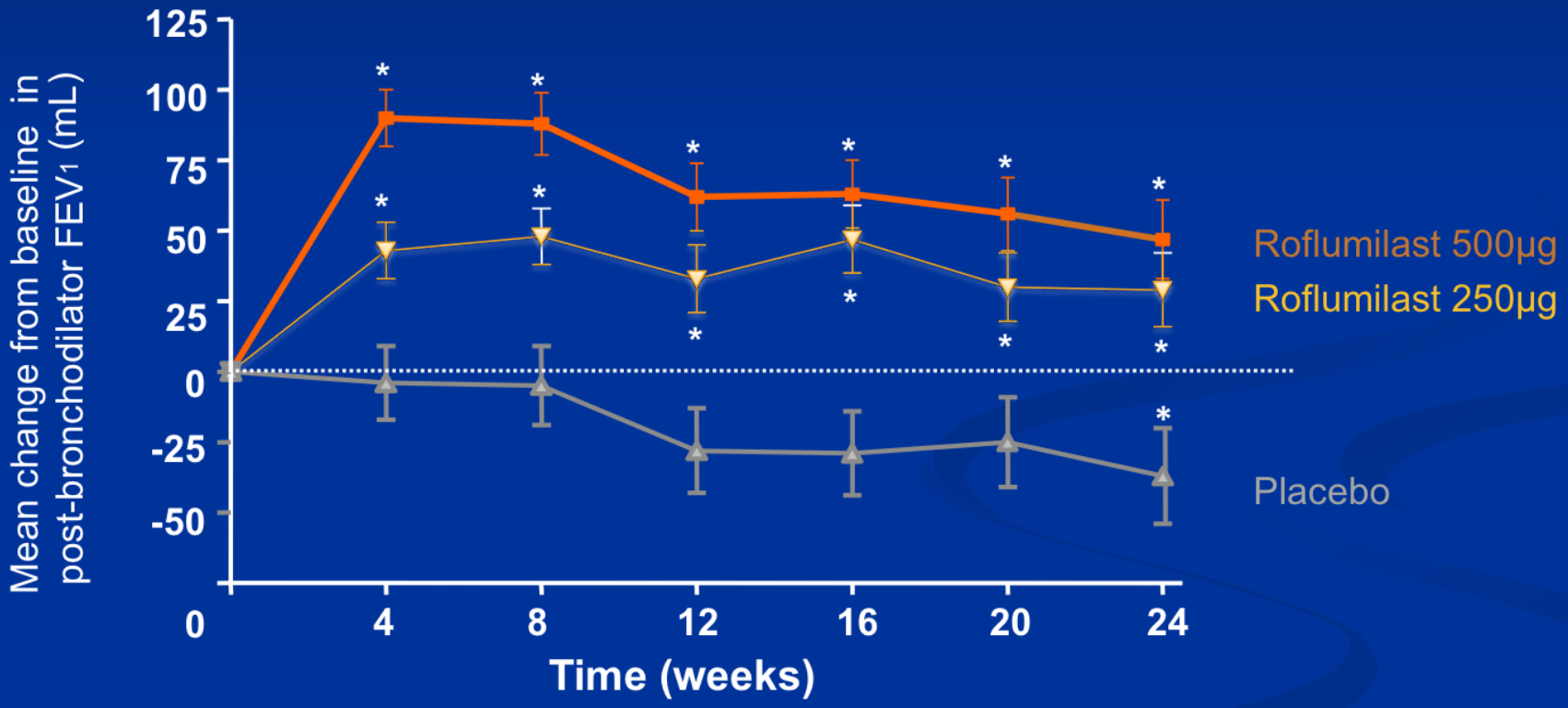

RISK*
(GOLD Classification of Airflow Limitation)
4
3
2
1
(C)
(D)
(A)
(B)
2 or more
Less than 2
RISK*
(Exacerbation history)
mMRC 0-1
CAT <10
mMRC ≥ 2
CAT ≥10
SYMPTOMS†
(mMRC or CAT score)

TORCH Study: All-cause Mortality at 3 Years



Calverley PM, et al. N Engl J Med 2007;356:775

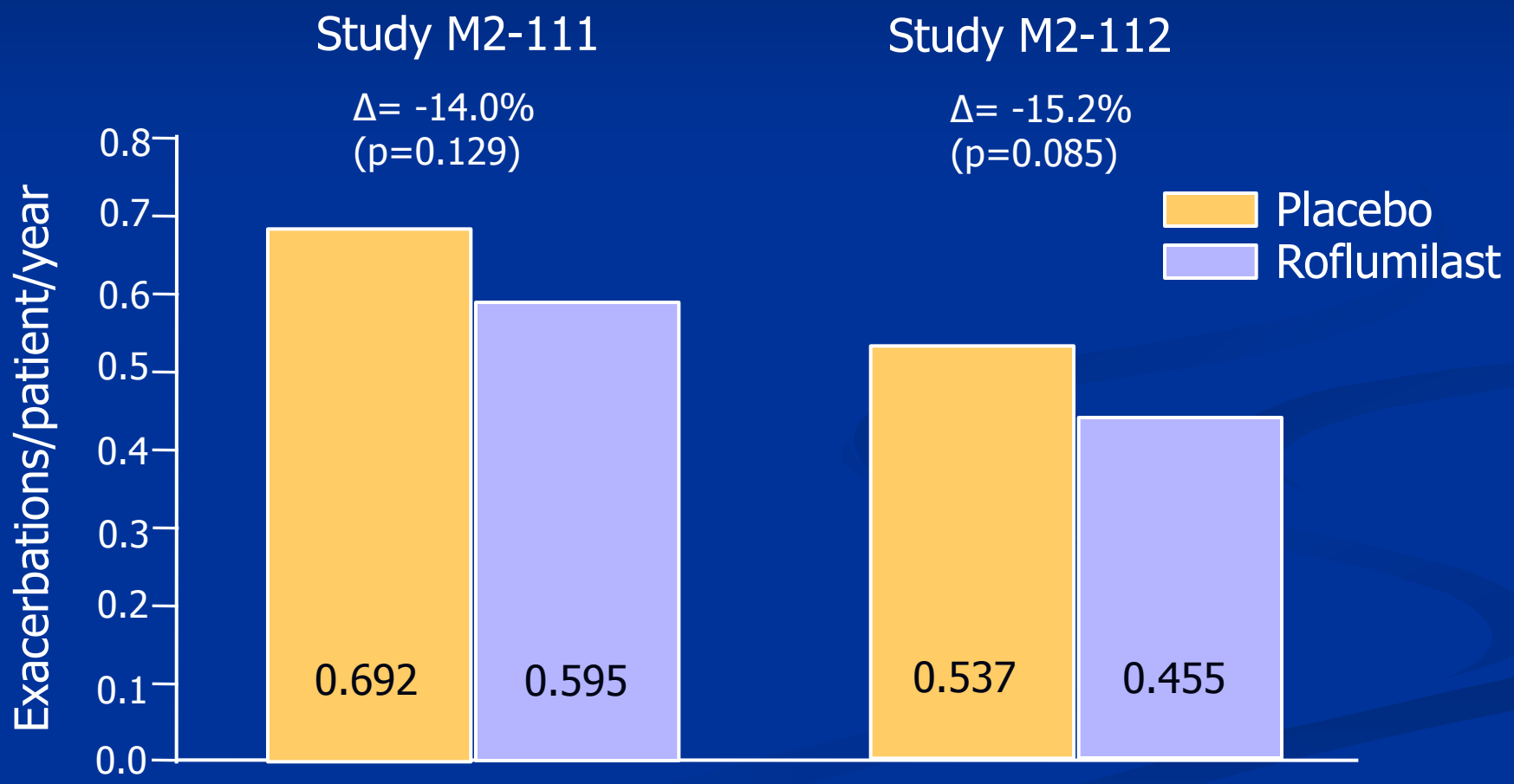
Roflumilast: Lung Function



* p<0.05 vs baseline

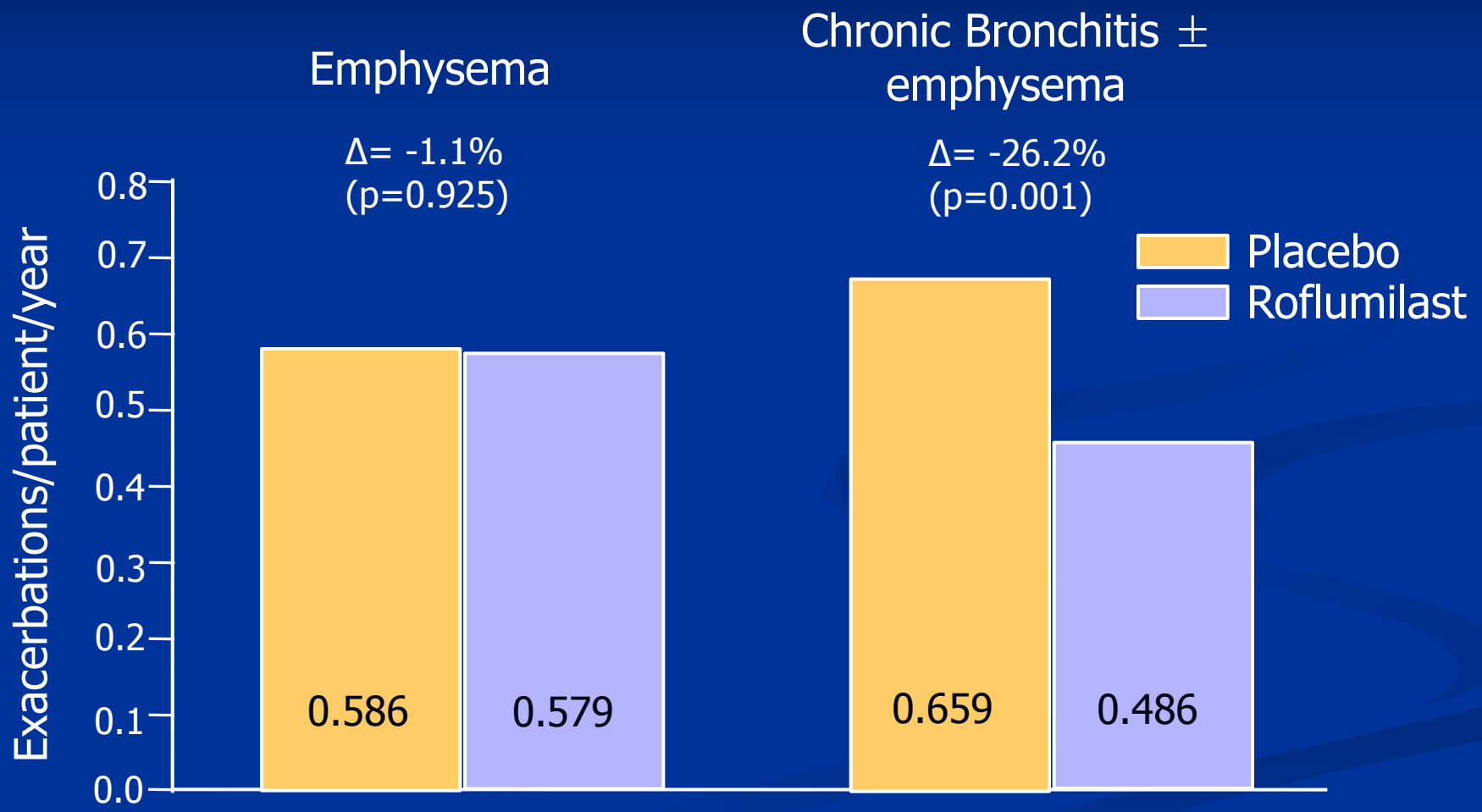
Rabe KF, et al. Lancet 2005;366:563

Roflumilast: Exacerbation Rate



Martinez FJ, et al. COPD7 2010; poster 12.

Roflumilast: Exacerbation Rate



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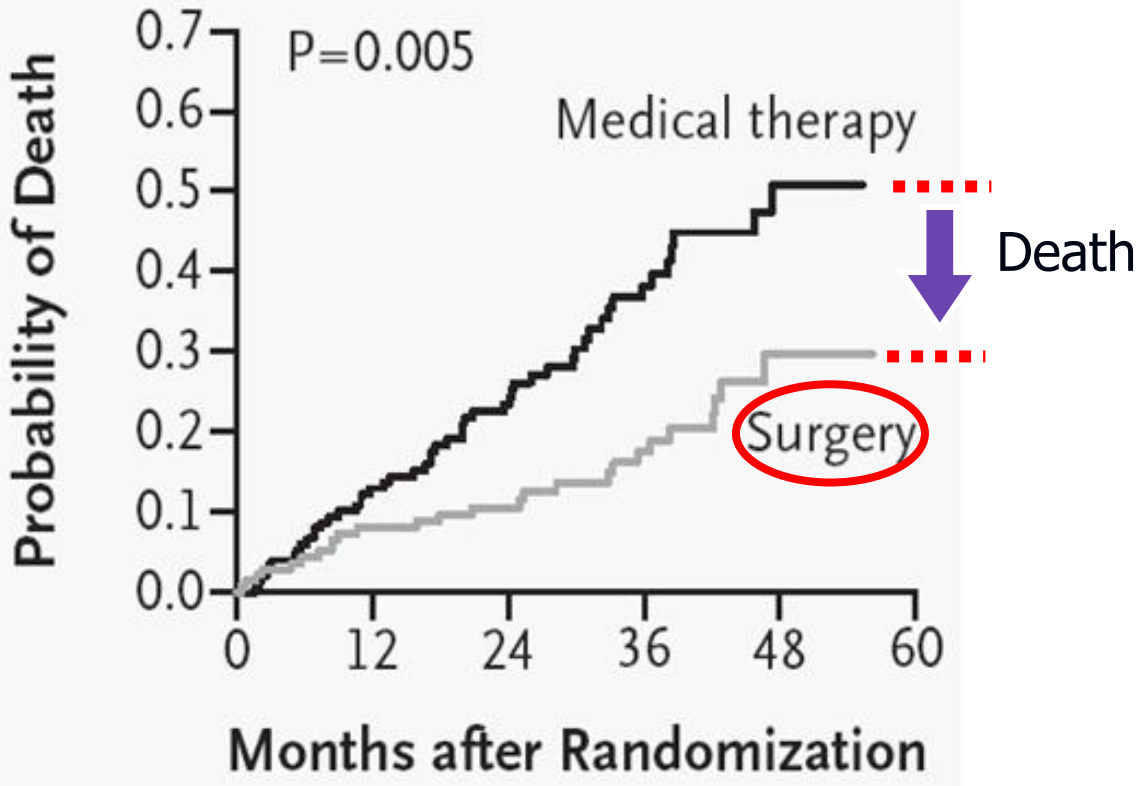
Lung Volume Reduction Surgery

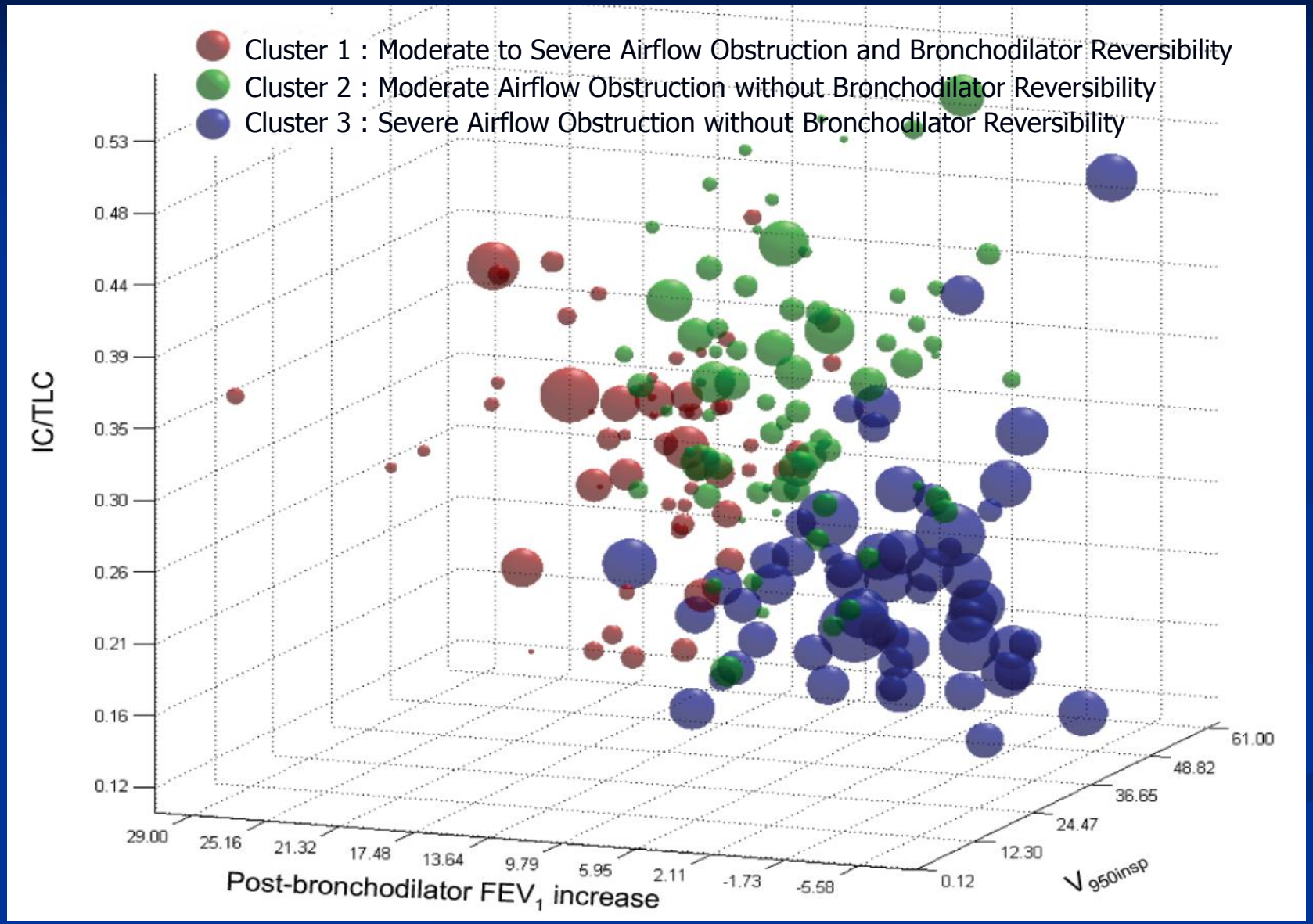
Emphysema: Upper-Lobe Predominance, Low Base-Line Exercise Capacity



No. at Risk					
Surgery	139	121	93	61	17
Medical therapy	151	120	85	43	13

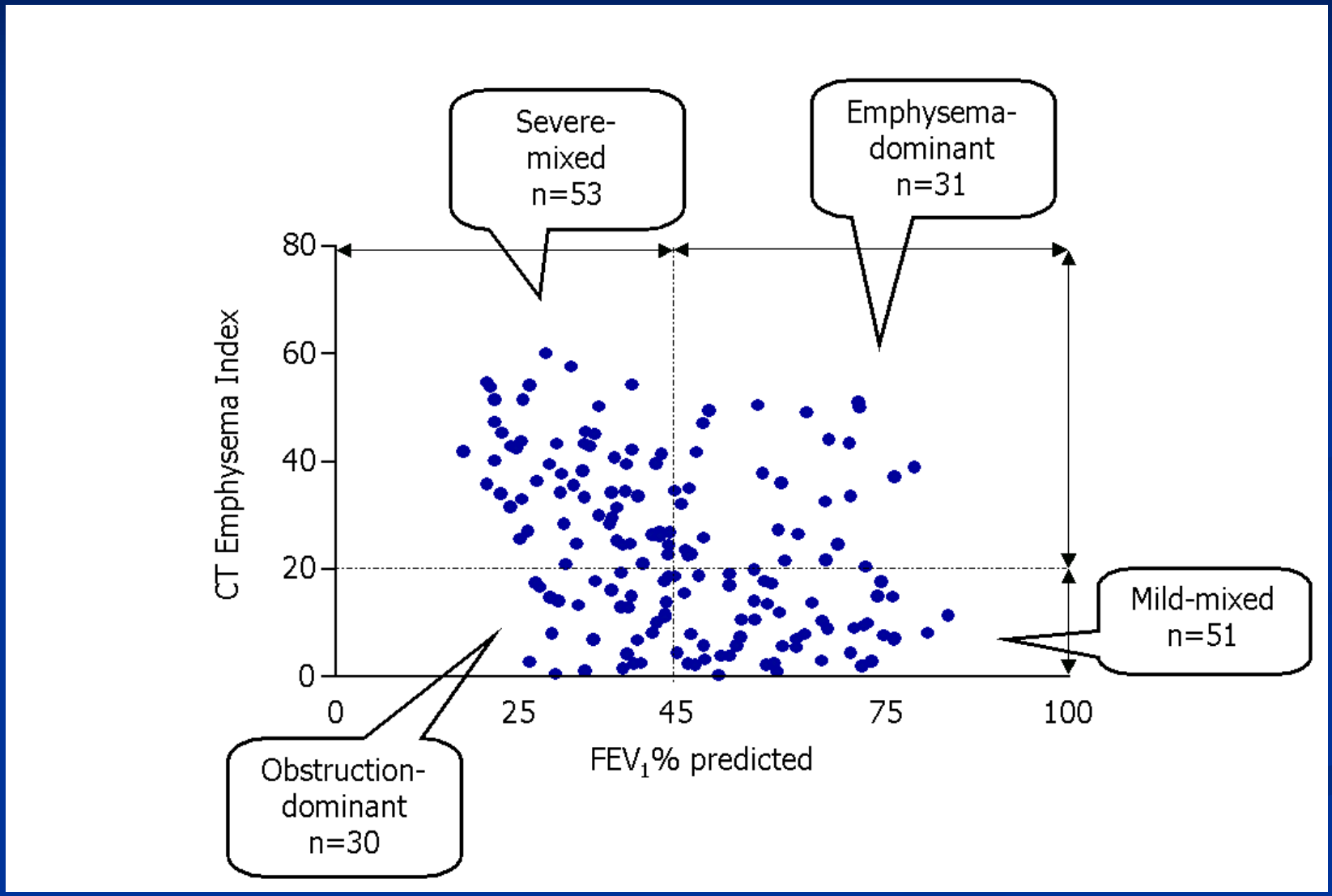
N Engl J Med 2003;348:2059

KOLD Cohort (n=191, age ≥60)



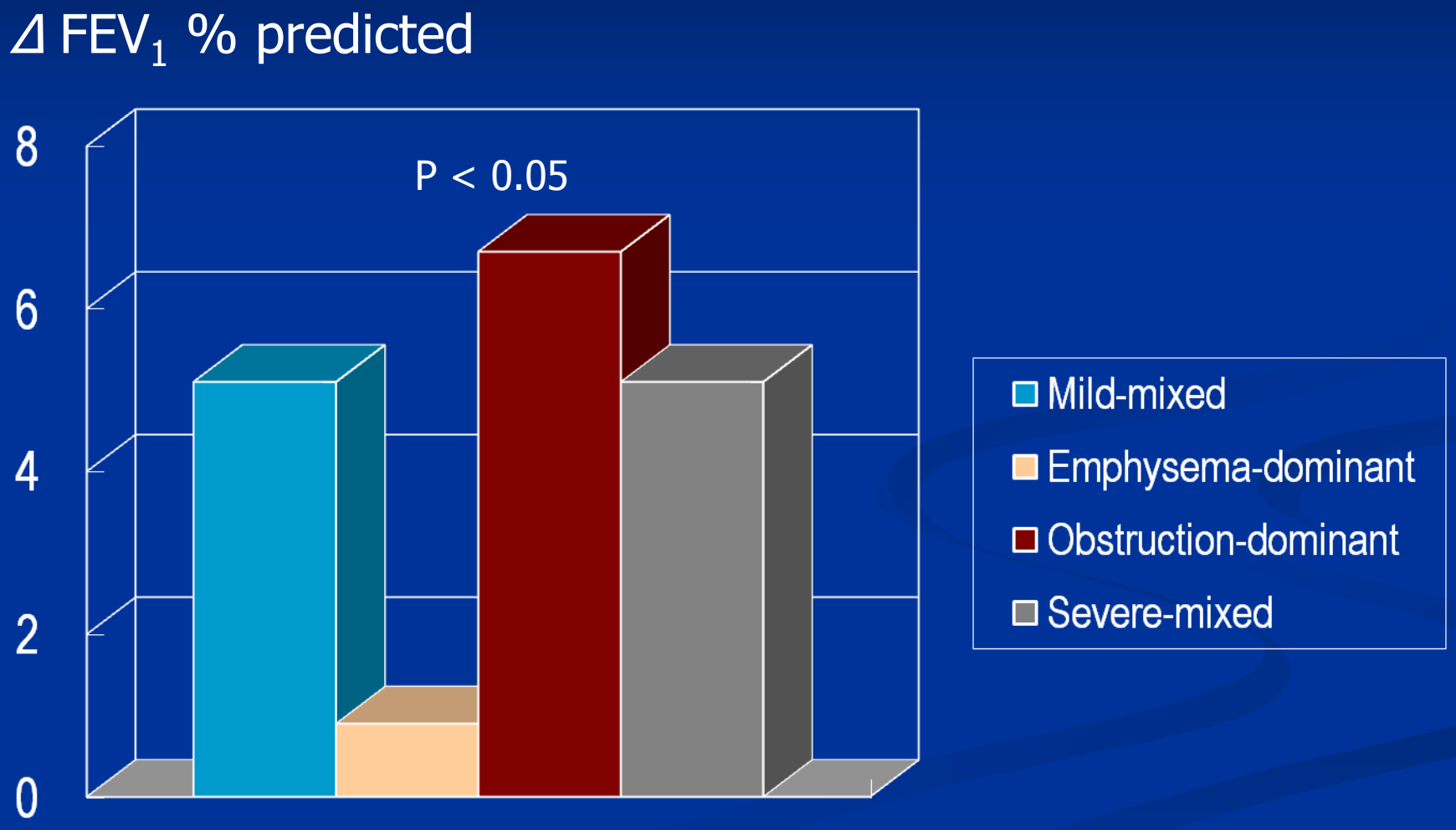
Jo KW et al. Int J Tuberc Lung Dis 2010;14:1481

Responses of Lung Function according to COPD Subtype



Lee JH, Respiratory Medicine. 2010: 104: 542

Reversibility after 3mo. with 'ICS & LABA'



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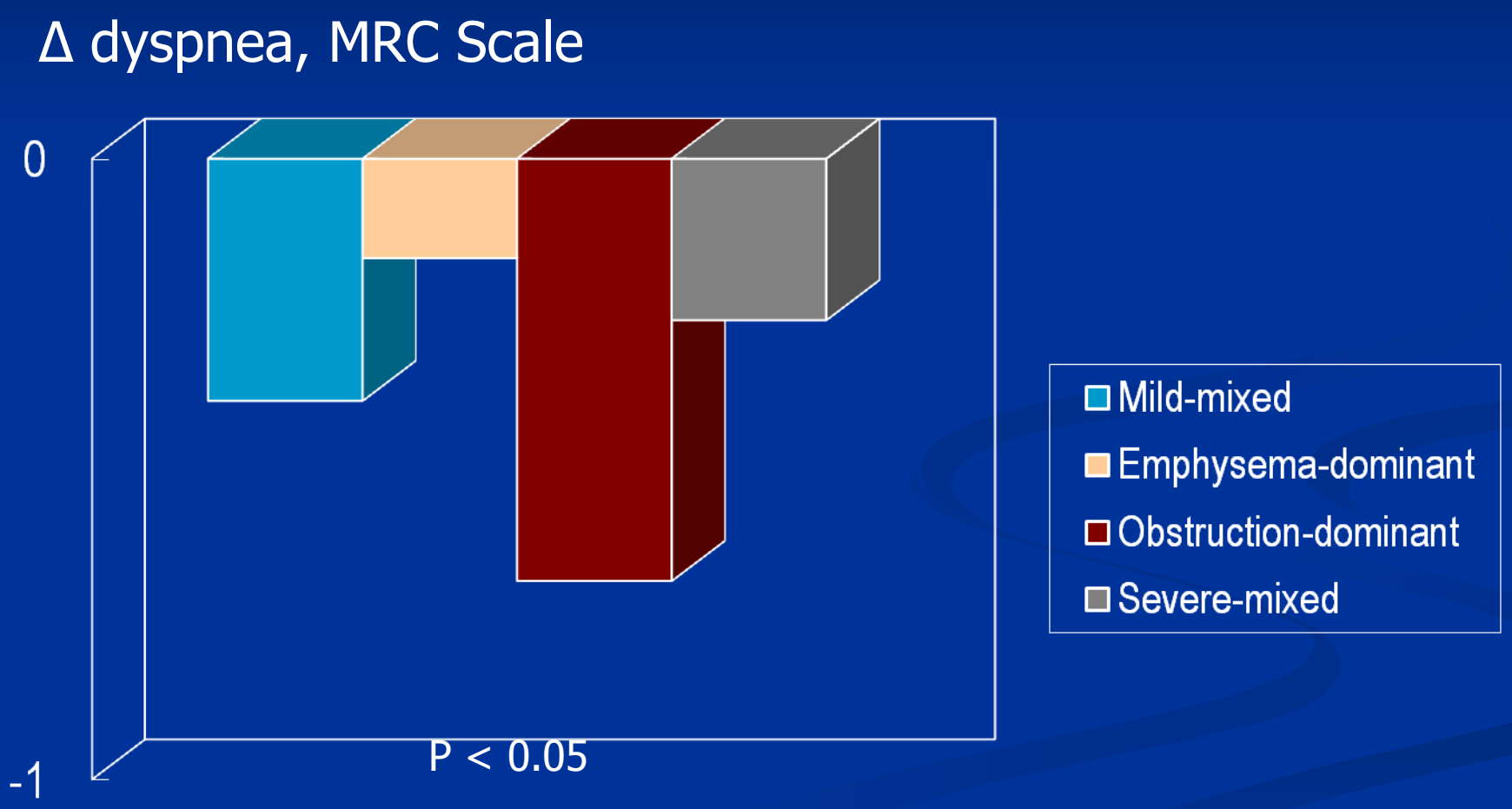

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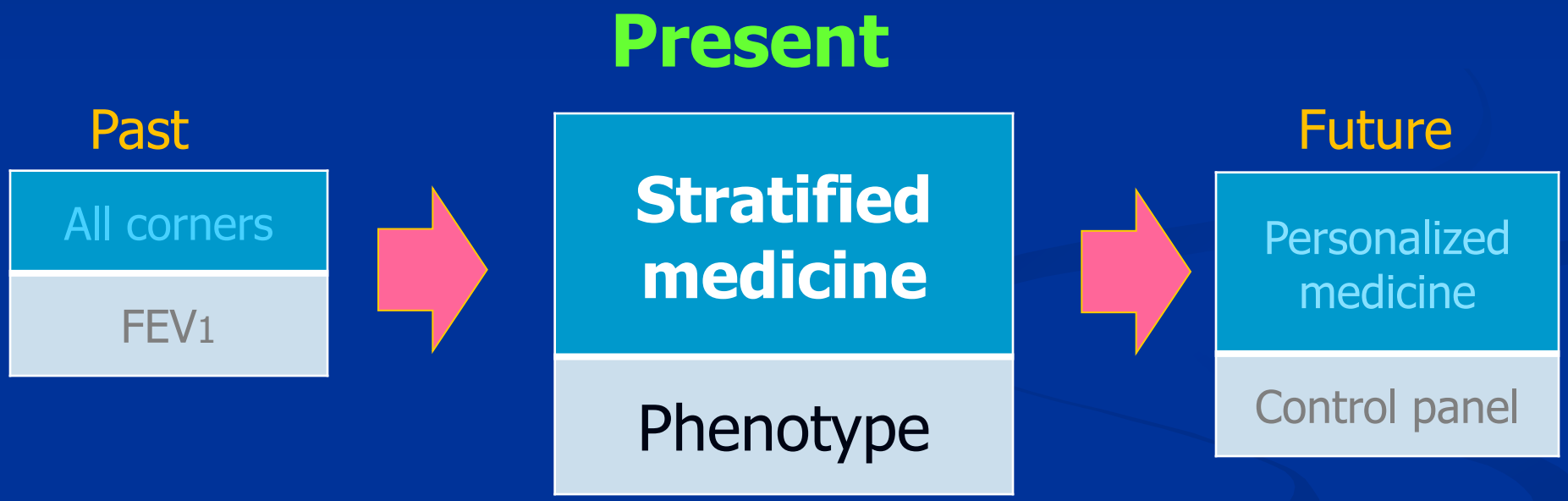
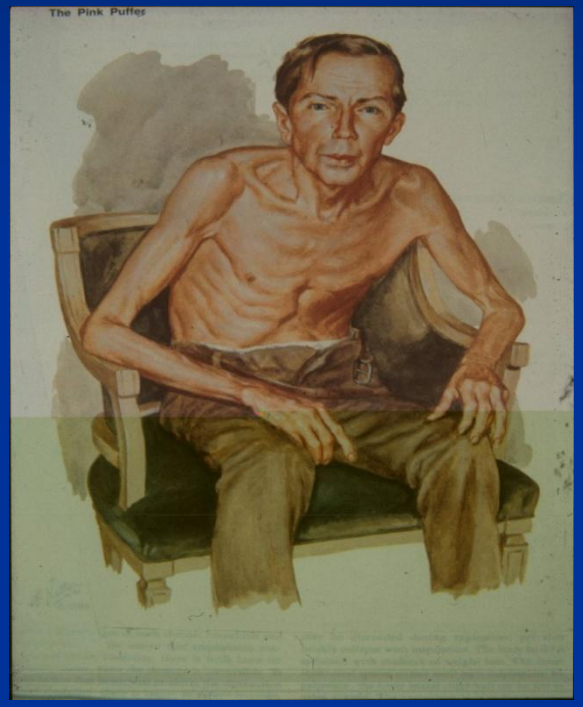
COPD Renaissance: Complexity, Phenotypes



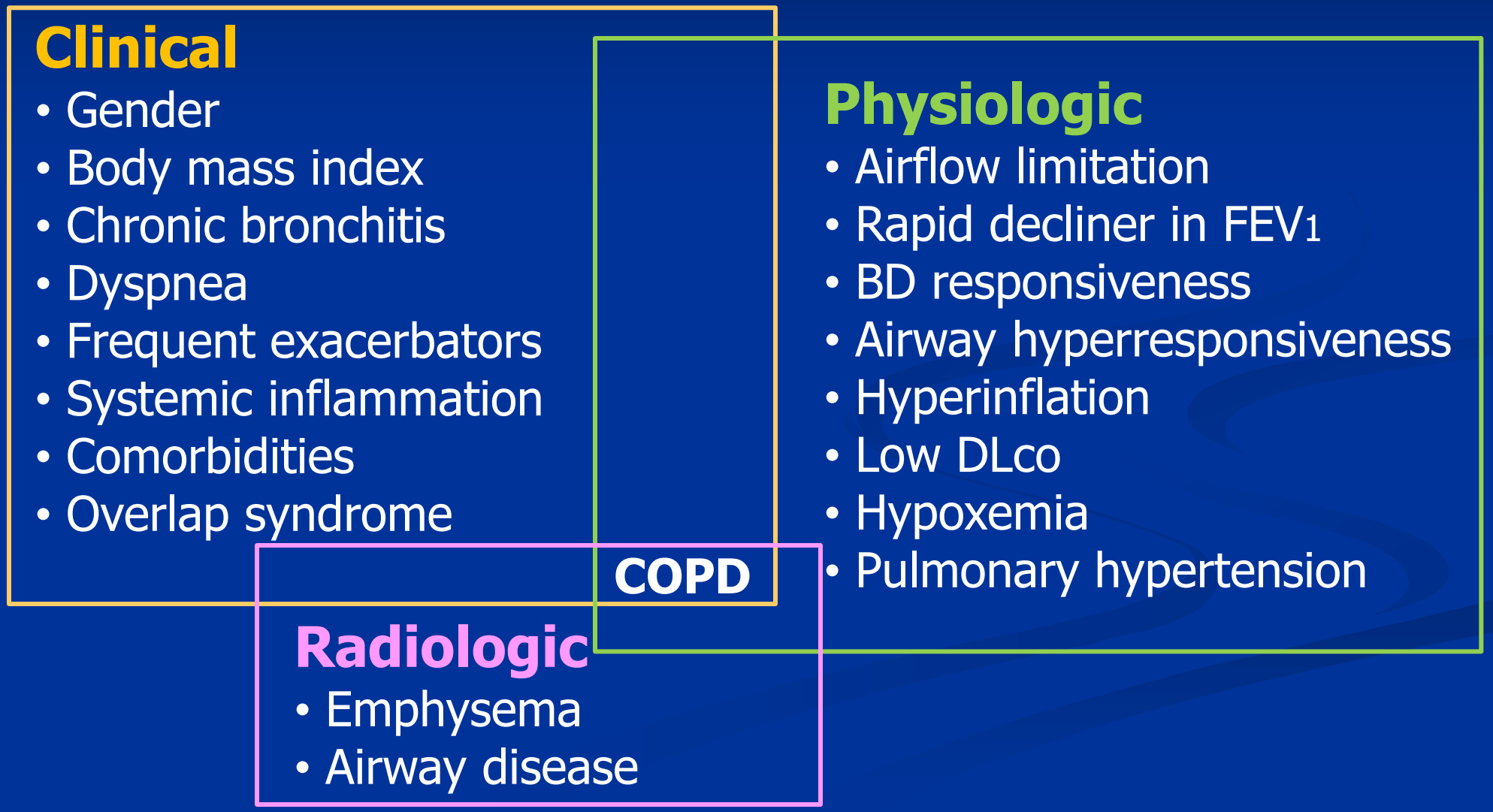
COPD Renaissance: Complexity, Phenotypes



Emphysema type
"pink puffer"
(thin and noncyanotic at rest)

Chronic bronchitis type
"blue bloaters"
(heavy and cyanotic)

COPD Renaissance: Complexity, Phenotypes



Gender: Women

- Greater risk of smoking-induced lung function impairment for the same level of tobacco exposure
  - More dyspnea and lower self-reported health status
  - Higher rates of exacerbation
  - Long-term oxygen therapy is less effective
  - Higher prevalence of anxiety

- Susceptibility to the effects of cigarette smoke
  Decreased clearance of the toxins
  Exaggerated immune and hormonal response

Gender: Women

- 2047 smokers in COPDGene

- Compared with men and women

  Individual assessment of multiple airways;

  trachea to sub-segmental airway

  Measured

  airway diameter

  airway lumen

  wall thickness

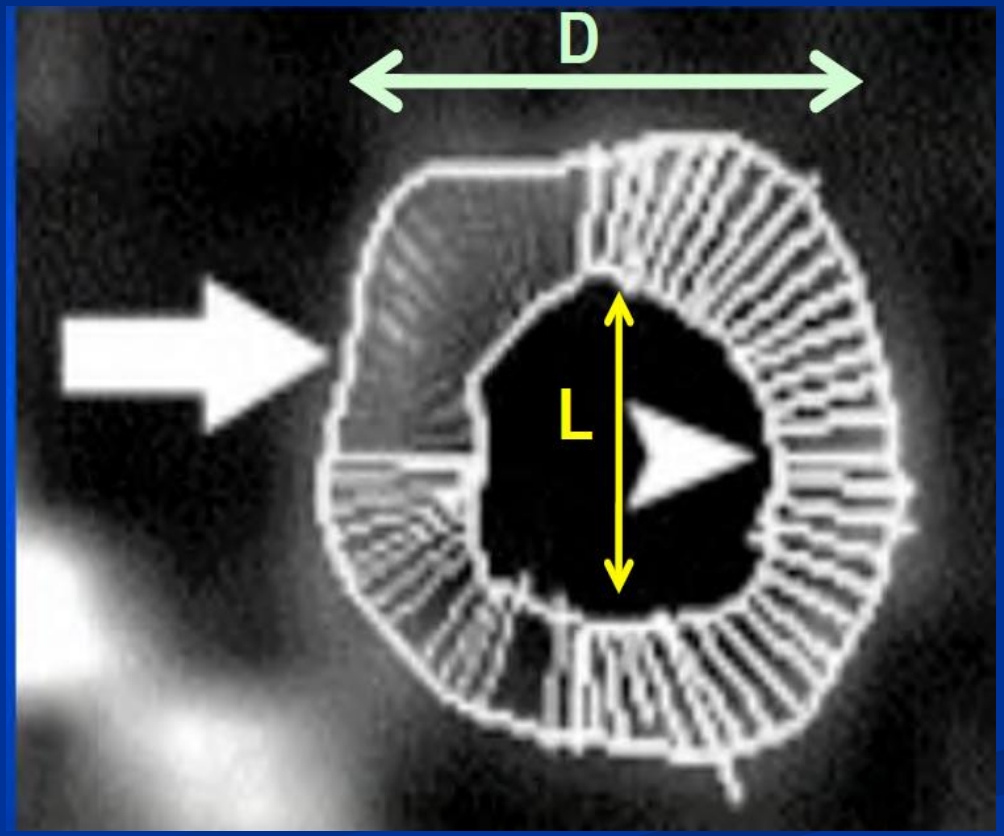
  wall area %

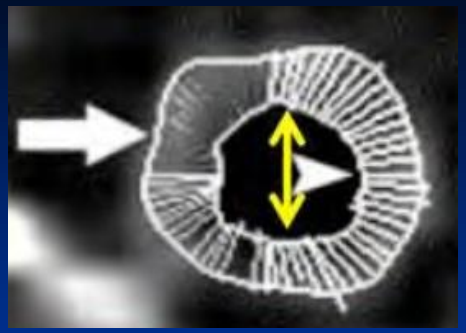
COPDGene
COPD Genetic Epidemiology

Kim YI et al. COPD 2011;8:285

Measures of Airway Wall Thickening

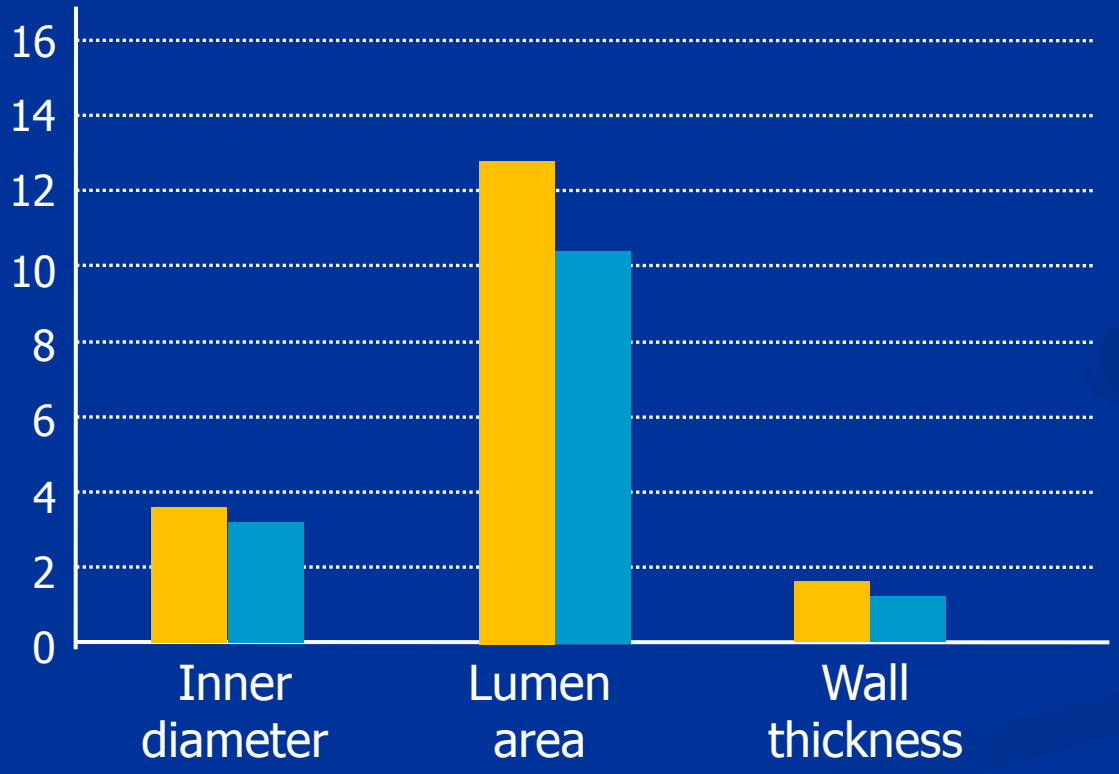
Airway lumen: L
Airway diameter: D
Airway thickness: D-L
Airway wall %
: wall area/total area bronchial X 100
AWT-Pi10
: square root of airway wall area of the airway with internal perimeter of 10mm

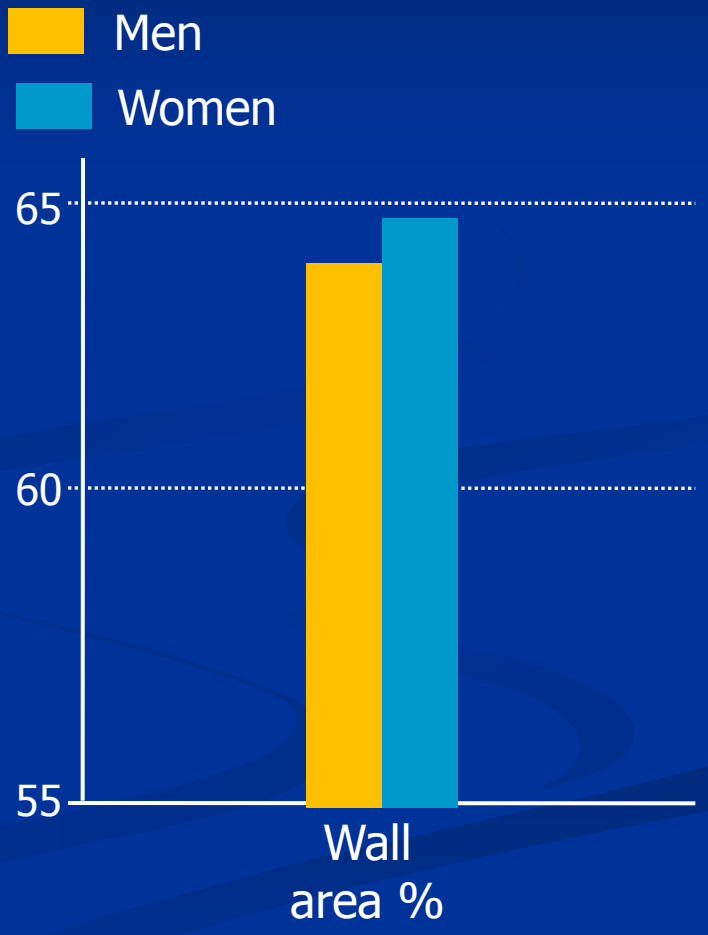




Airway Dimensions by Gender

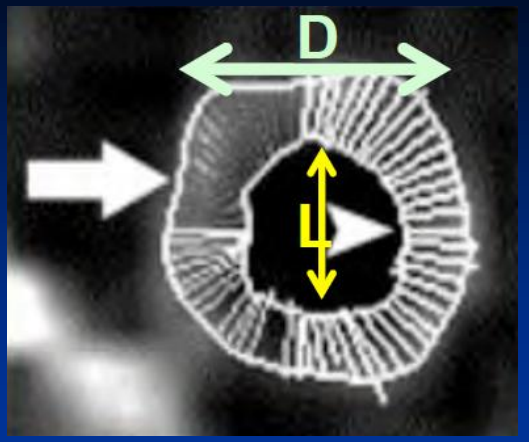
All p<0.001





Kim YI et al. COPD 2011;8:285

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

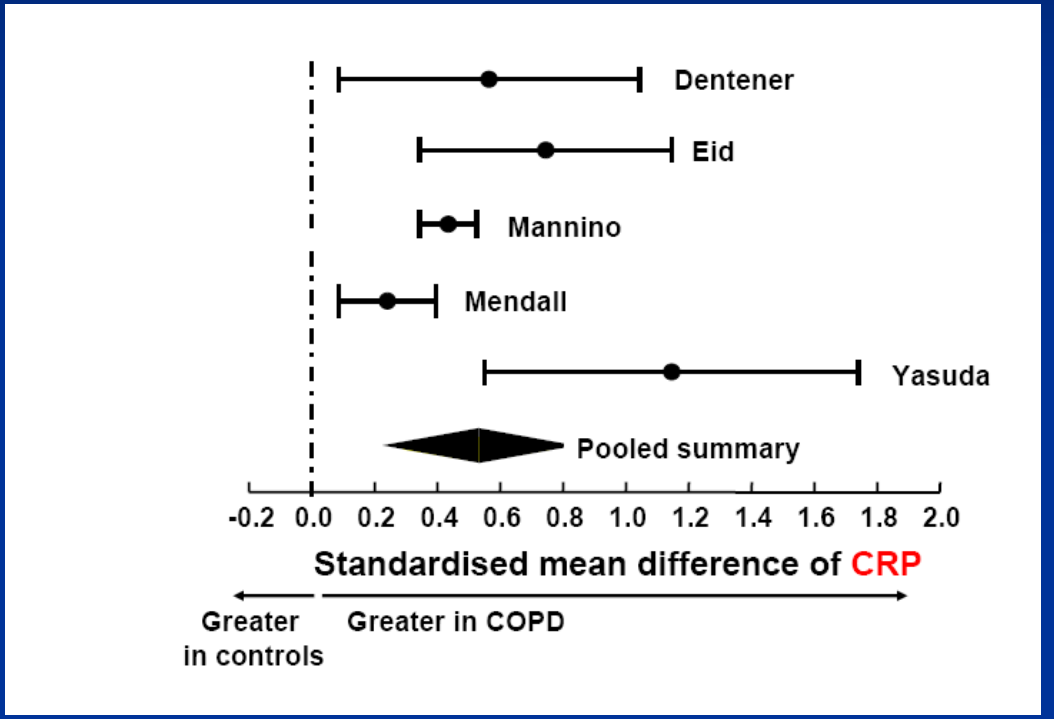
COPDGene
COPD Genetic Epidemiology

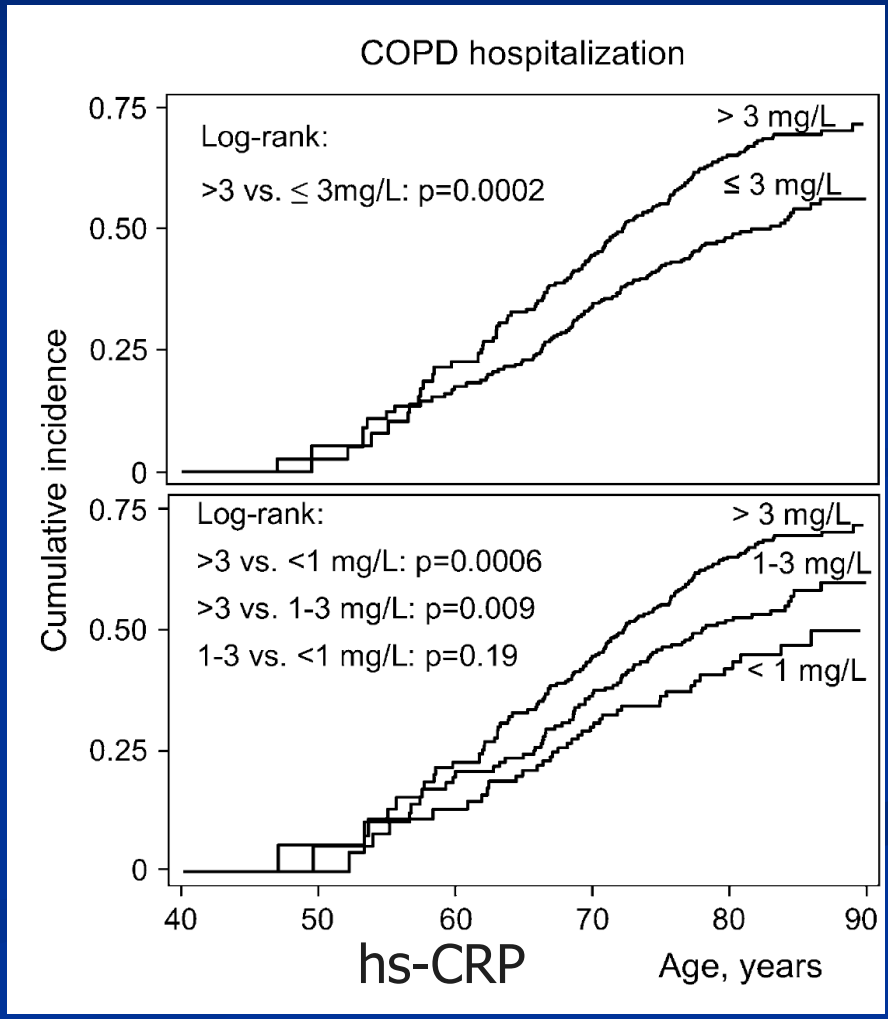
Kim YI et al. COPD 2011;8:285

Inflammation: Pulmonary, Systemic

- Common preventable and treatable disease
- Characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases

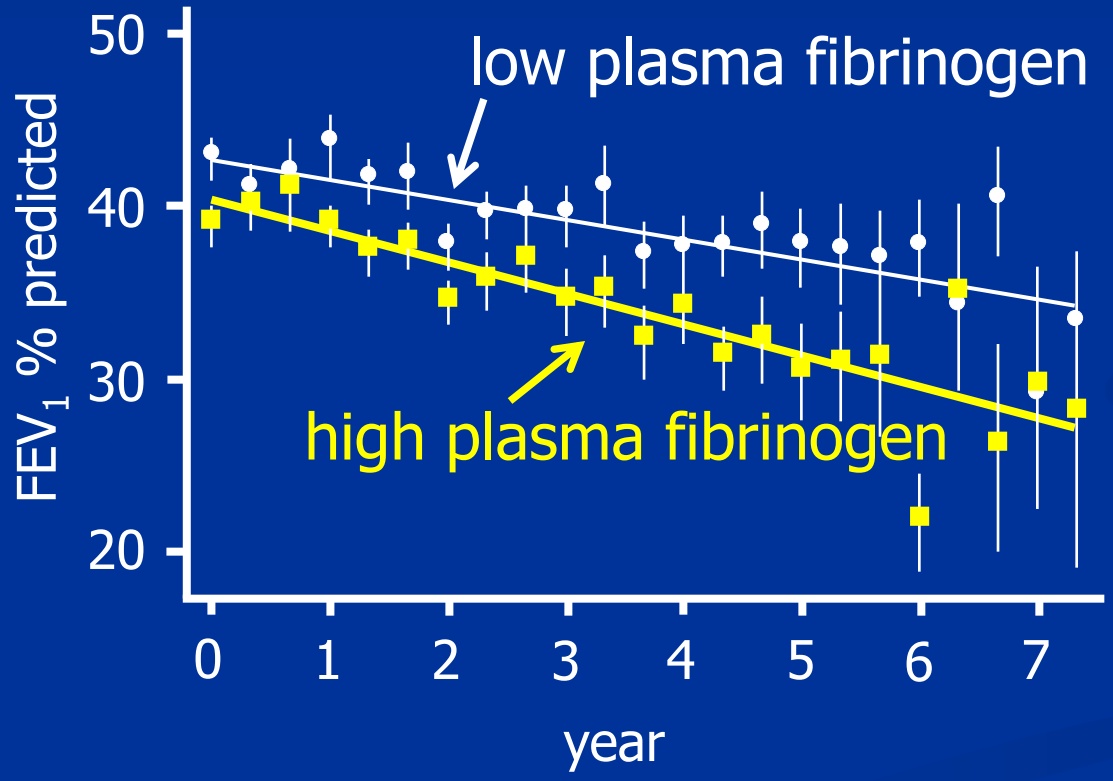
Systemic Inflammation, CRP

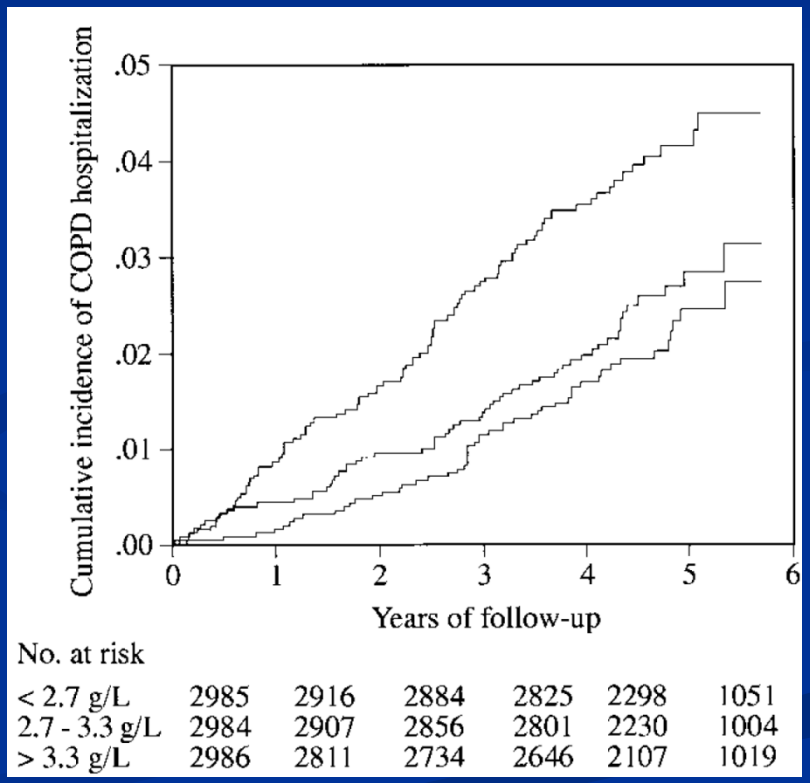




Dahl et al. AJRCCM 2007.

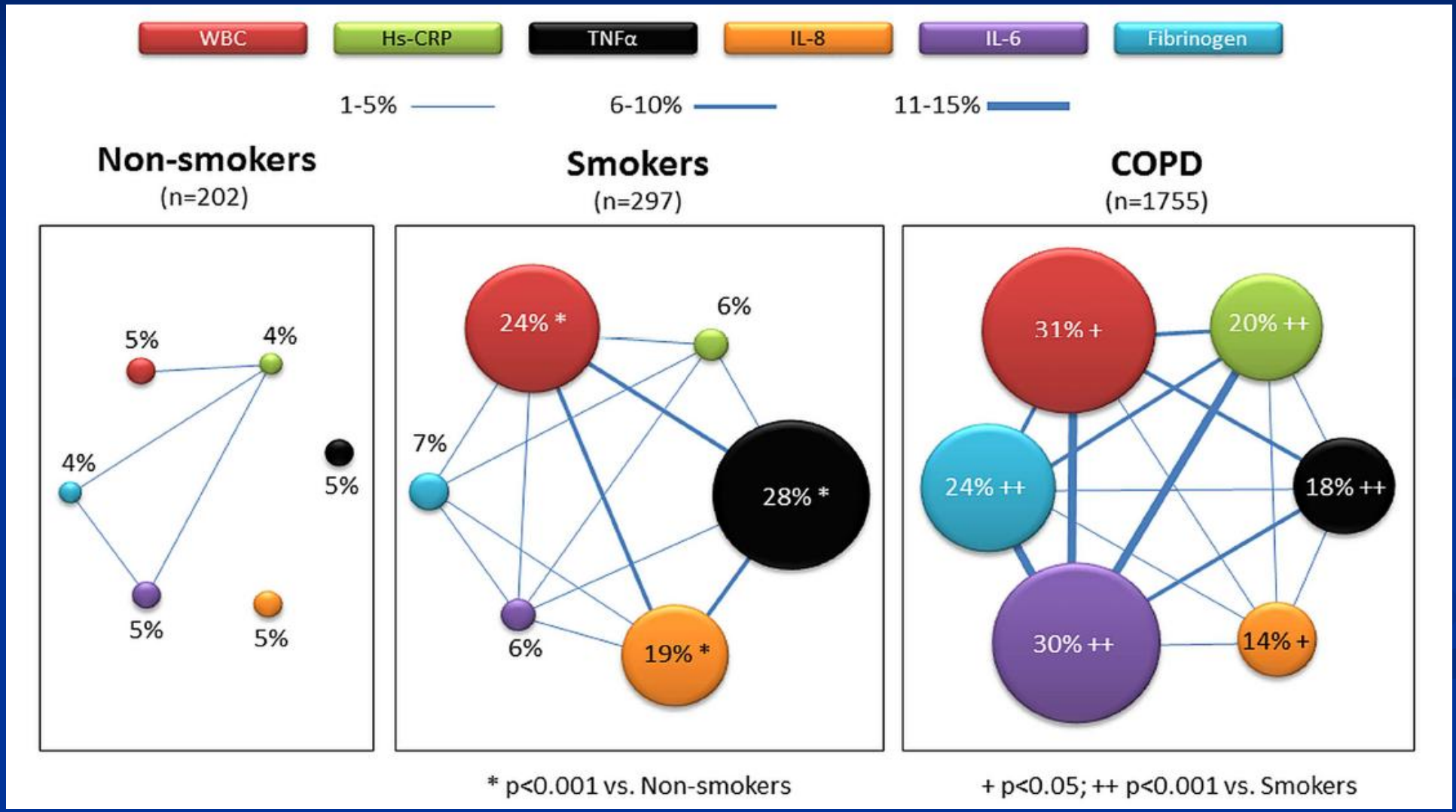
Systemic Inflammation, Fibrinogen





Fibrinogen

Inflammation: Pulmonary, Systemic



Inflammation: Pulmonary, Systemic

- Not all patients with COPD have persistent systemic inflammation (A third of COPD appear to be persistently non-inflamed)
- Persistent inflammation had more frequent exacerbations and a six times higher mortality during 3 years of follow-up than patients without inflammation
- 'Inflammometry' has now been used in pilot studies to guide therapy in COPD with very encouraging results
  - Sputum eosinophil: ICS 500 g bid
  - Sputum neutrophil: azithromycin 250mg for 3 month
  - Systemic inflammation(CRP>3 mg/L): simvastatin 20 mg for 3 month

Inflammation: Pulmonary, Systemic

- Common preventable and treatable disease
- Characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases

- No specific recommendations
  - how to measure and monitor inflammation
  - what therapeutic alternatives should be used based on the assessment of abnormal inflammatory response

- Inflammatory markers will sooner or later be included in the routine management of patients with COPD

Chronic Airway 'Colonization'

- Healthy lungs display a complex 'microbiome'
  : Microbiome changes in many diseases including COPD

- Influence of changes in the lung microbiome
  - Increasing the symptoms (cough and expectoration)
  - Frequent exacerbations, accelerating rate of FEV_1 decline
  - Predisposition to lung cancer
  - Relationship with pulmonary and systemic inflammation

- Current recommendations do not mention when and how this should be diagnosed, monitored or treated

Overlap syndrome (ACOS)

Diagnostic criteria

Two major criteria or one major with two minor criteria

Major criteria
- Marked reversibility with bronchodilators >15 % and > 400 ml in FEV_1)
- History of asthma (<40 year of age)
- Sputum eosinophilia

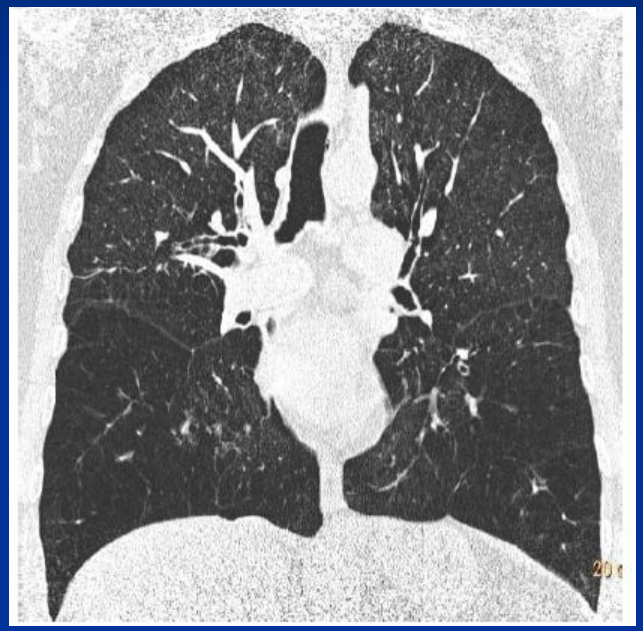
Minor criteria
- Reversibility on two separate occasions (>12 % and >200 ml in FEV_1)
- History of atopy
- Increased total serum IgE

Overlap syndrome (ACOS)

- Frequent exacerbations, poor quality of life
- Rapid decline in lung function
- High mortality

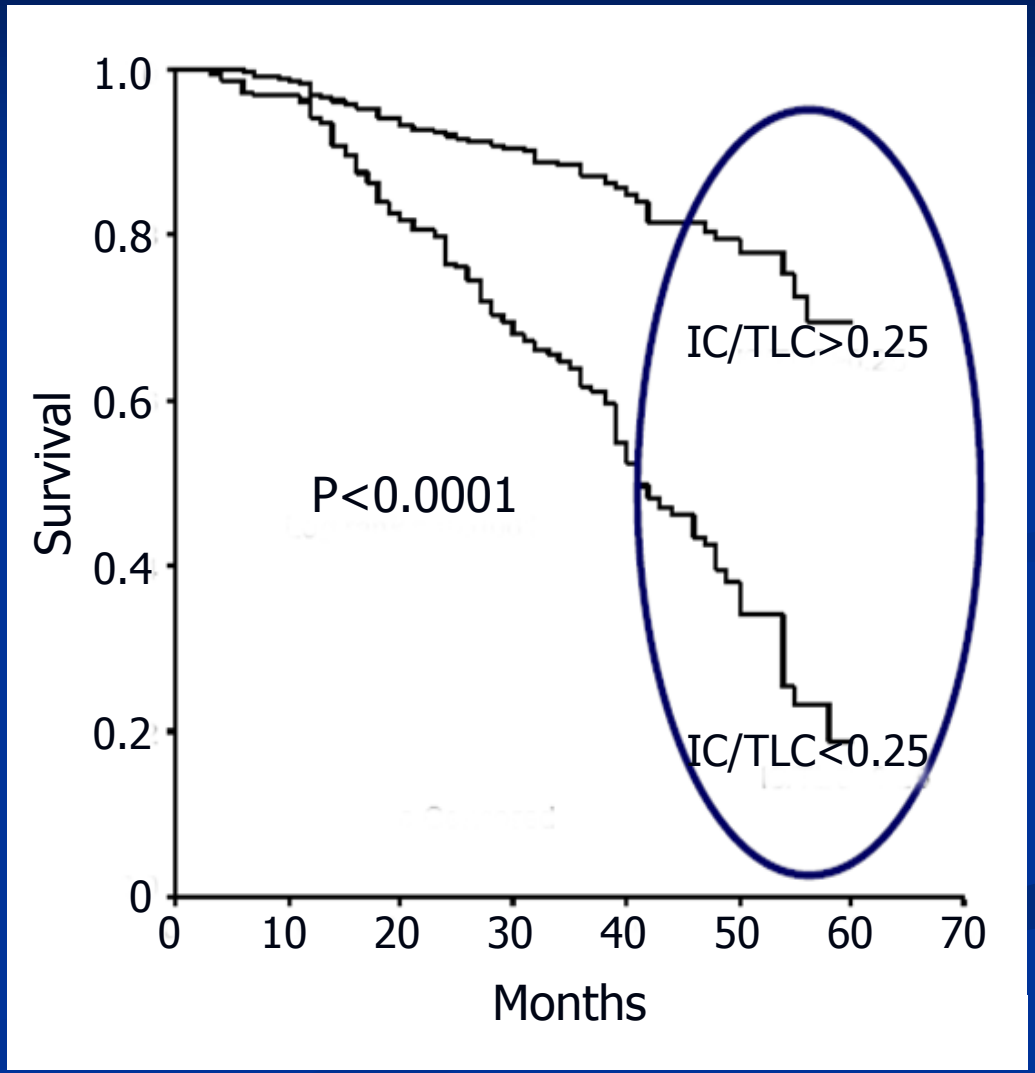
- Overlap syndrome can develop due to an accelerated decline in lung function or incomplete lung growth in children
  : Risk factor
  - increasing age
  - bronchial hyper-responsiveness
  - tobacco smoke exposure
  - asthma
  - lower respiratory infections/exacerbations

Hyperinflation



n = 689

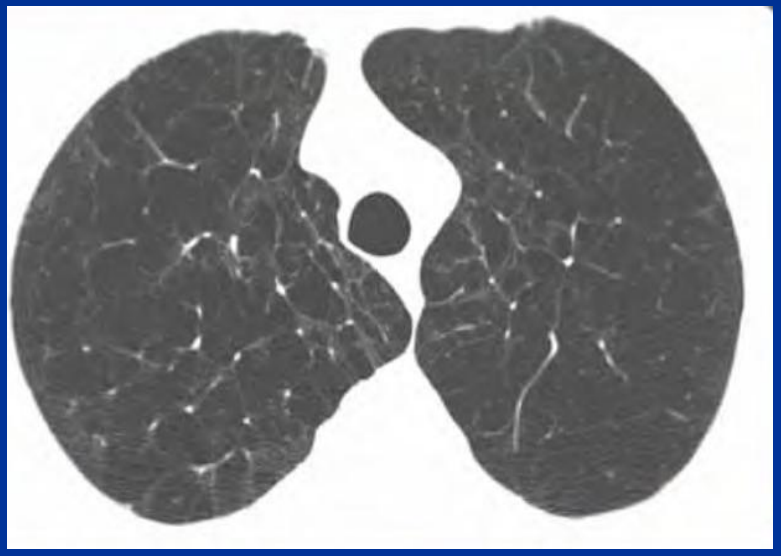
Median F/U = 34 months



Casanova, et al. Am J Respir Crit Care Med. 2005; 17:591

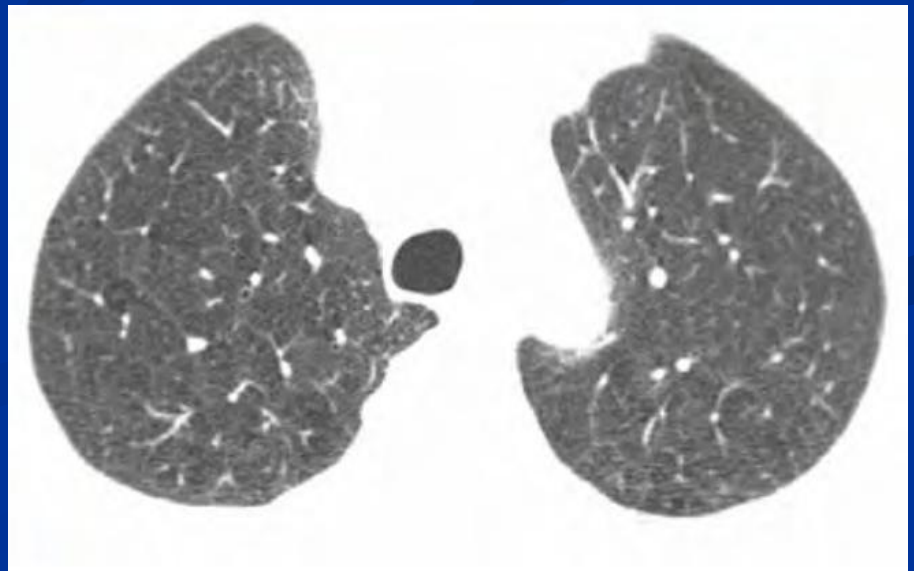
Chest CT Scan

GOLD Stage 2 COPD - FEV_1 60% Predicted



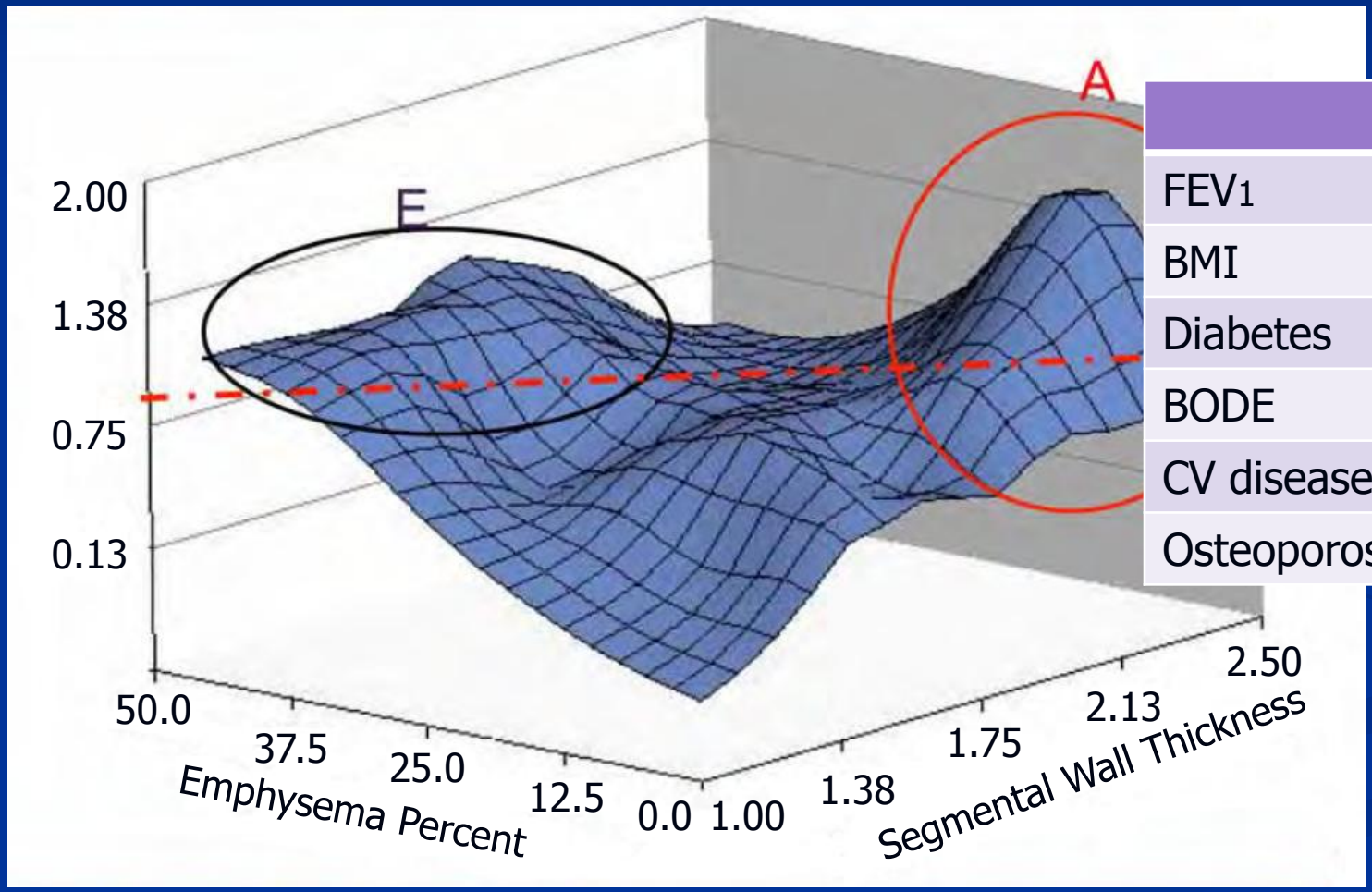
Patient 1:
Marked Panlobular Emphysema

Patient 2:
Minimal Emphysema



Chest CT Scan : Emphysema

COPD Exacerbation in the COPDGene Study



	Emphy	Airway
FEV_1	29%	51%
BMI	22.7	30.7
Diabetes	9.7%	19.5%
BODE	5.1	3.0
CV disease	9.5%	12.1%
Osteoporosis	28.0%	7.8%

Han MK et al. Radiology 2011;26:274

Chest CT Scan : Emphysema

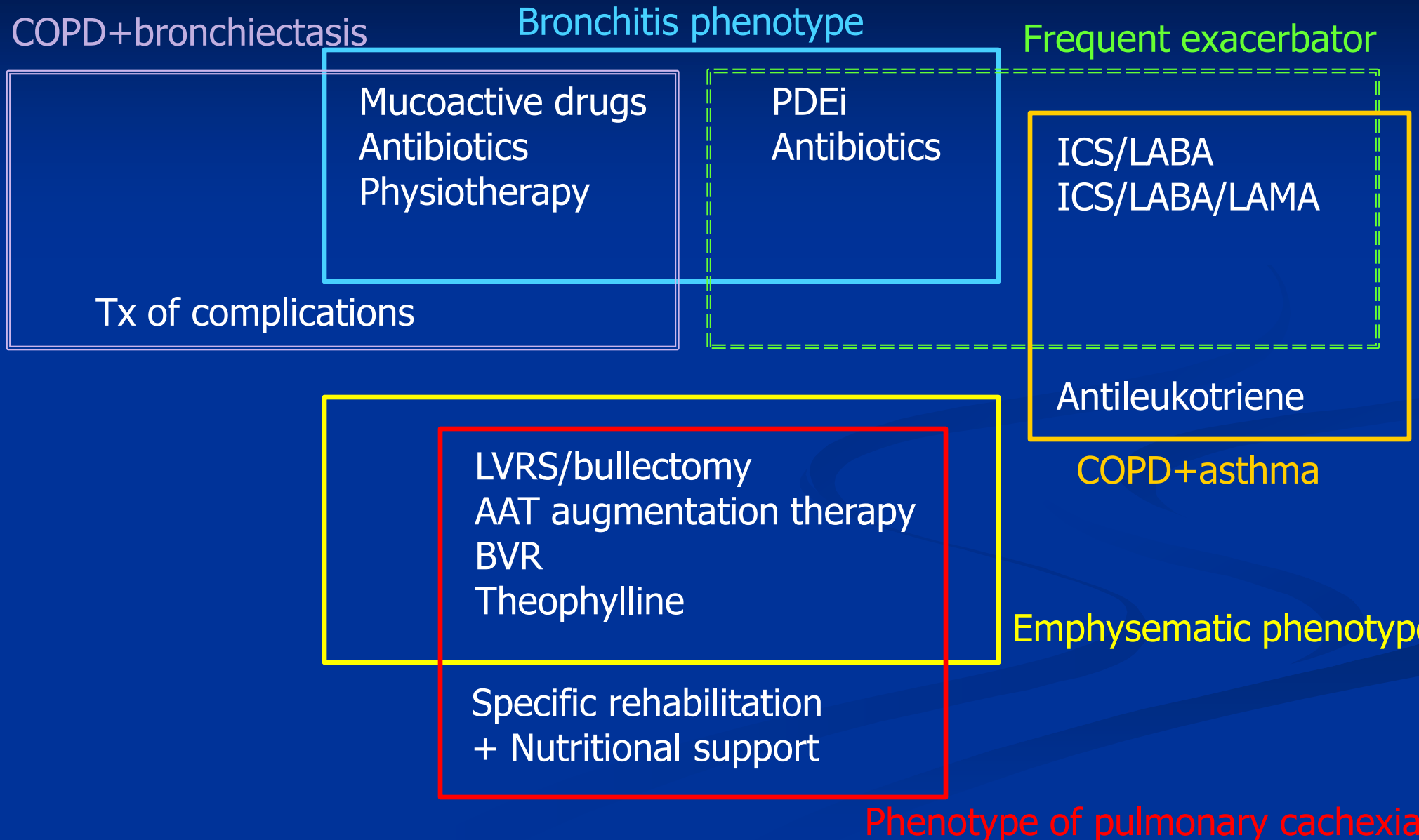
COPD Exacerbation in the COPDGene Study

- Bronchial wall thickness and emphysema percentage are associated with exacerbation frequency
- 1.84 fold AECOPD increase per 1 mm increase in bronchial wall thickness (not airway wall %)
- 1.18 fold AECOPD increase per 5% increase in patients with emphysema>35%

Quantitative CT can help identify subgroups of patients with COPD who experience exacerbations for targeted research and therapy development for individual phenotypes

Han MK et al. Radiology 2011;26:274

Phenotype-specific COPD Treatment



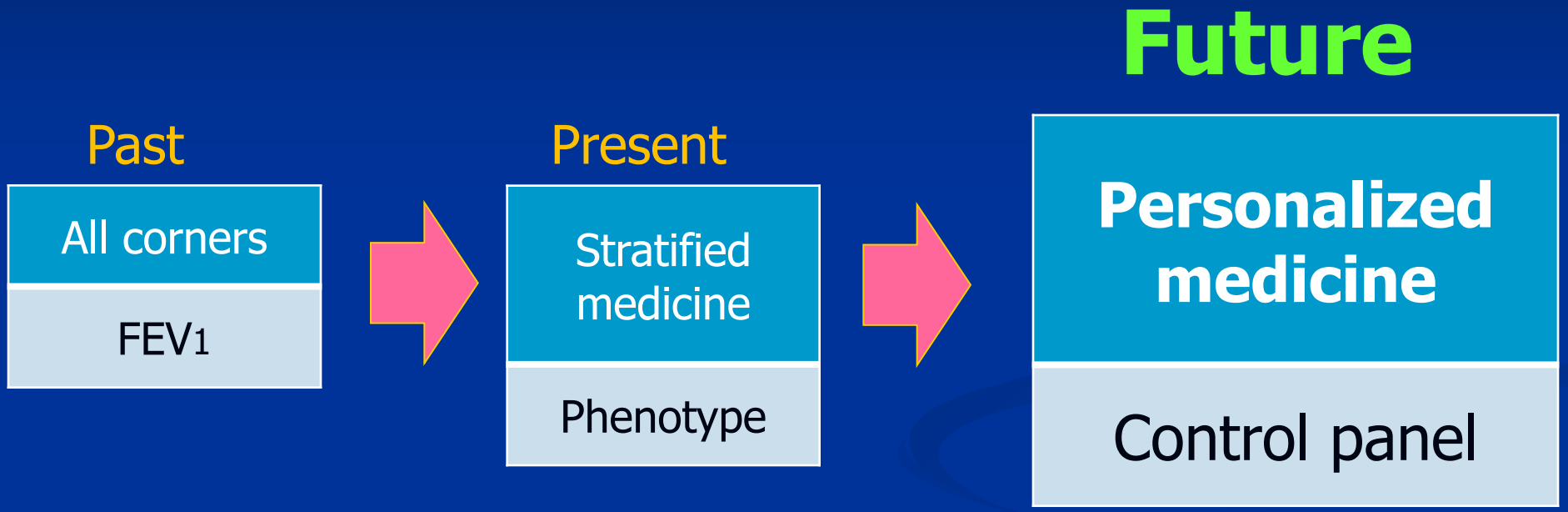
Phenotypes and Clinical relevance in COPD

Phenotypes	Symptoms or quality of life	Exacerbations	Rate of disease progression	Mortality	Targeted interventions
Clinical					
Female sex	Poor	Frequent		Low	Smoking cessation
Low BMI	Poor		Rapid	High	Nutrition, rehabilitation
Chronic bronchitis	Poor	Frequent	Rapid	High	PDE-4 inhibitor
Dyspnea	Poor	Frequent		High	BD, rehabilitation
Frequent exacerbator	Poor	Frequent	Rapid	High	Smoking cessation, vaccination, BD, ICS, PDE-4 inhibitor
Comorbidities					
Skeletal muscle wasting	Poor	Frequent		High	Rehabilitation
Cardiovascular		Frequent		High	Statin, ACEi or ARB
Osteoporosis	Poor			High	Specific therapy
Anxiety and depression	Poor	Frequent		High	Specific therapy
Overlap syndrome	Poor	Frequent	Rapid	High	BD, ICS

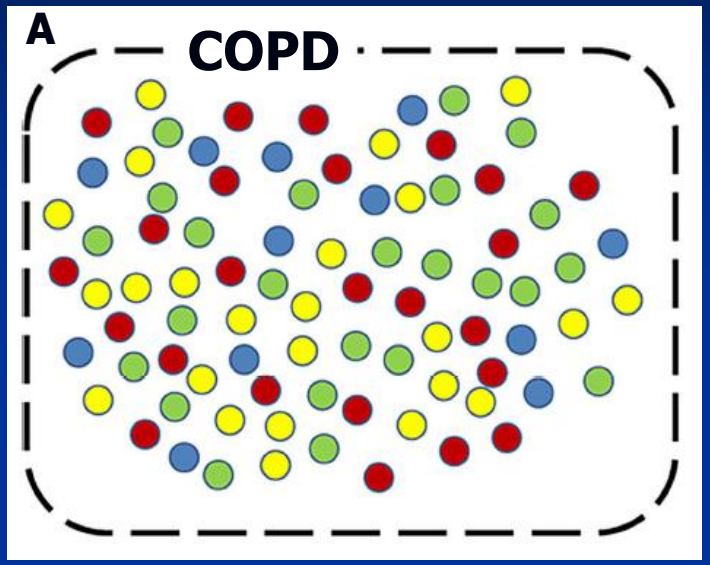
Phenotypes and Clinical relevance in COPD

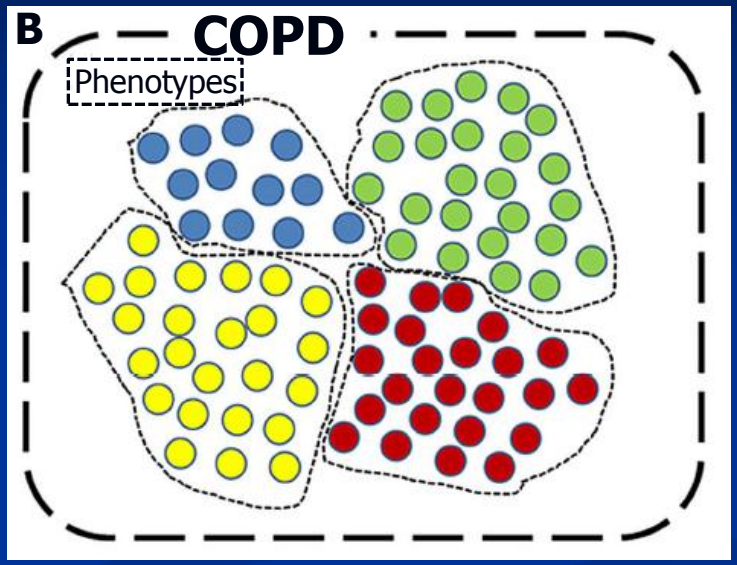
Phenotypes	Symptoms or quality of life	Exacerbations	Rate of disease progression	Mortality	Targeted interventions
Physiologic					
Degree of airflow limitation	Weak correlation	Frequent		High	BD, ICS, PDE-4 inhibitor
Rapid decliner			Rapid	High	Smoking cessation
AHR			Rapid		BD, ICS
Hyperinflation	Poor			High	BD
Low DL_{CO}	Poor			High	Avoid LVRS
PAH	Poor			High	Endothelin receptor antagonist, PDE-4 inhibitor, statin
Hypoxemia	Poor			High	LTOT
Radiologic					
Emphysema	Poor	Frequent	Rapid	High	LVRS, AAT replacement
Airway disease	Poor	Frequent			BD

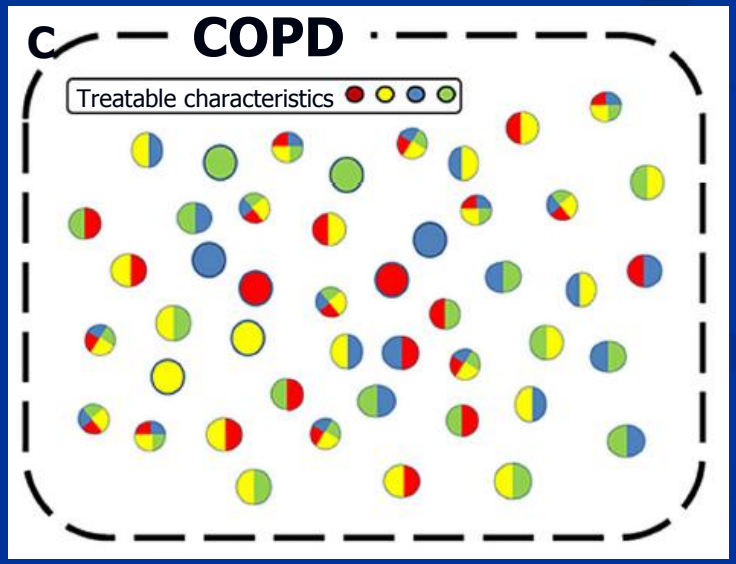
COPD Future: Personalized Medicine



COPD Future: Personalized Medicine

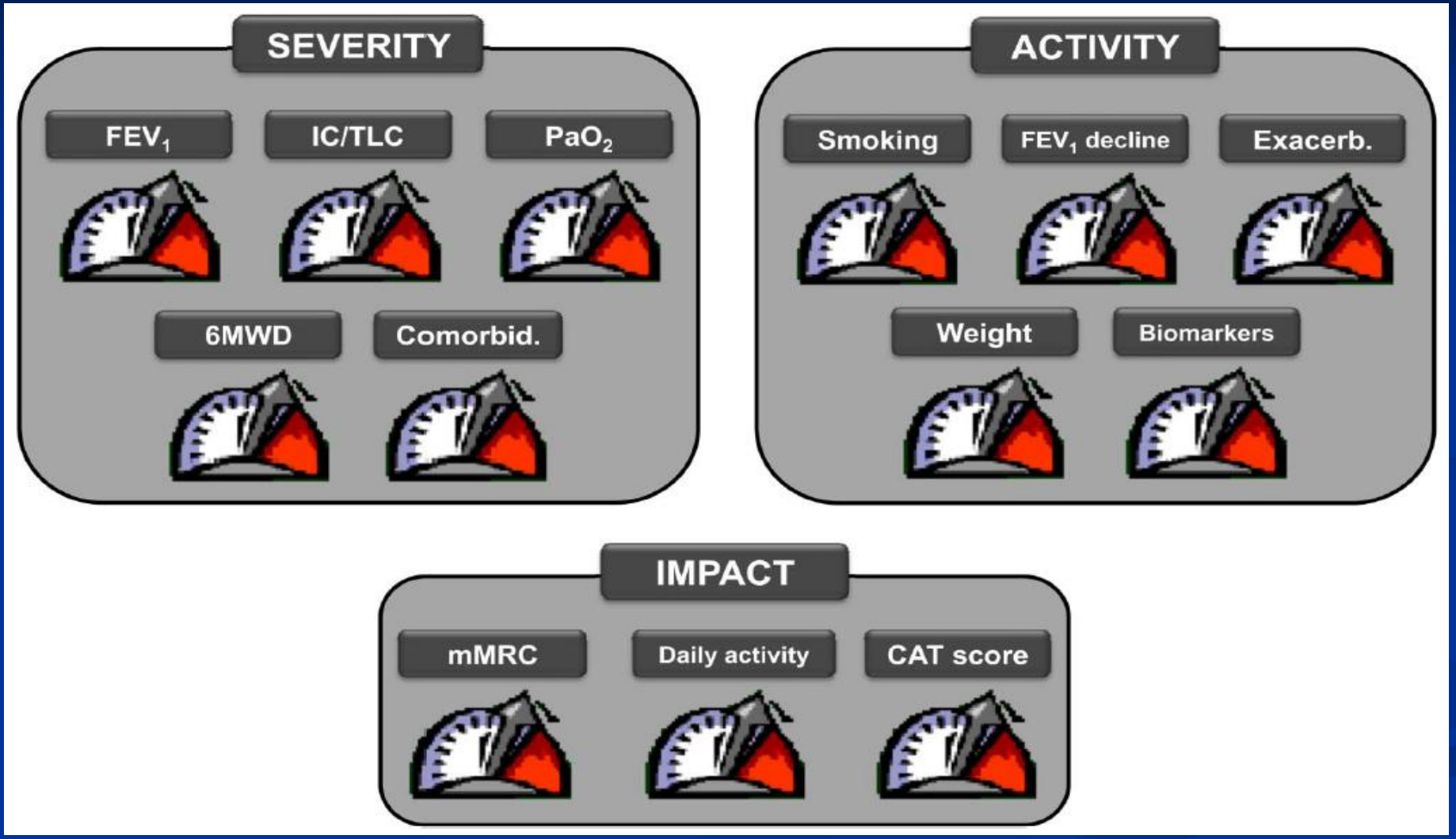






COPD Future: Personalized Medicine

COPD Control Panel



Severity: extent of functional loss of the target organ
Activity: level of activation of the biological process that drive disease progression

COPD Future: Personalized Medicine

Severity (Mild)

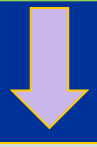
- GOLD grade II
- no hyperinflation
- normal PaO_2
- normal exercise tolerance
- no comorbidities

Impact (Low)

- normal mMRC
- normal CAT scores
- normal daily activity

Activity (High)

- current smoker
- increased FEV_1 decline with two exacerbations over the past 6 months
- raised levels of biomarker of disease activity



Therapeutic intervention (anti-inflammatory therapy?) prevents future progression of the disease

COPD Future: Personalized Medicine

Severity (Severe)

- FEV1<50% predicted
- hyperinflation
- low exercise capacity
- comorbidities (cardiovascular, obesity)

Impact (High)

- high mMRC
- low CAT scores
- house bound

Activity (Low)

- ex- smoker
- constant FEV_1
- no exacerbations
- stable BMI
- normal biomarker of disease activity

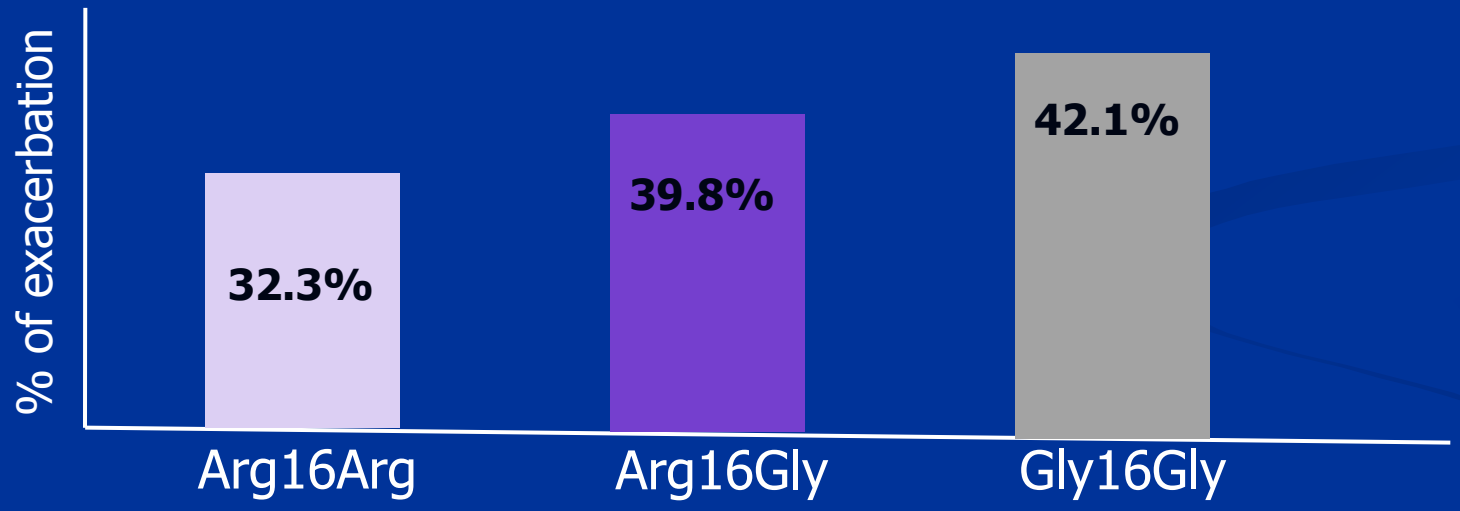
Bronchodilator treatment, treat comorbidities, rehabilitation but may question the need for anti-inflammatory therapy

COPD Future: Personalized Medicine

β_2-adrenergic receptor (ADRB2) polymorphisms

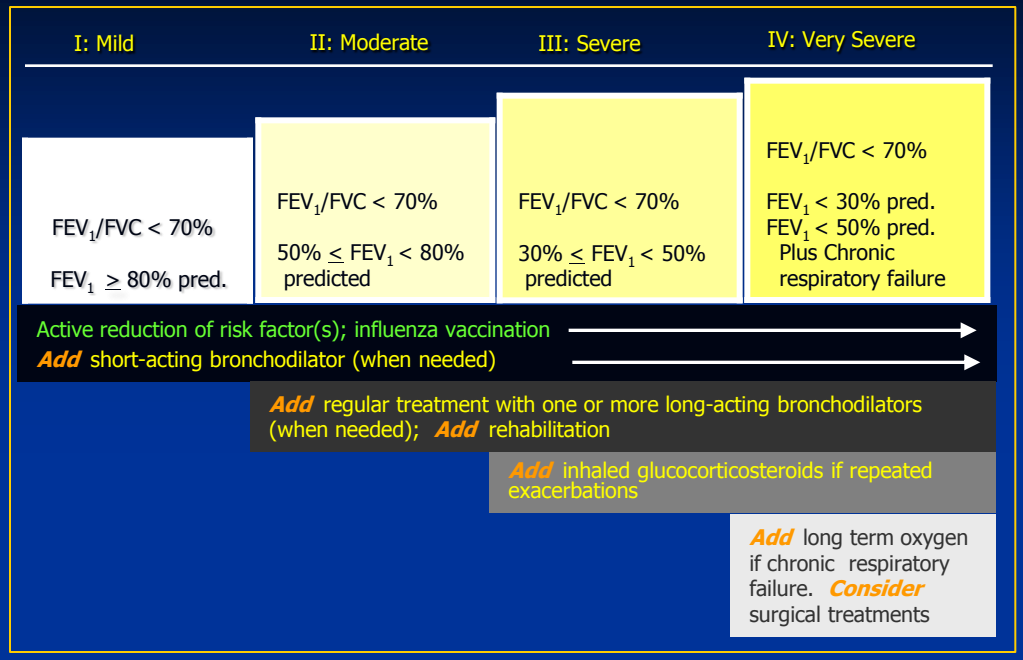
- Salmeterol group

  Proportion of patients with at least one exacerbation

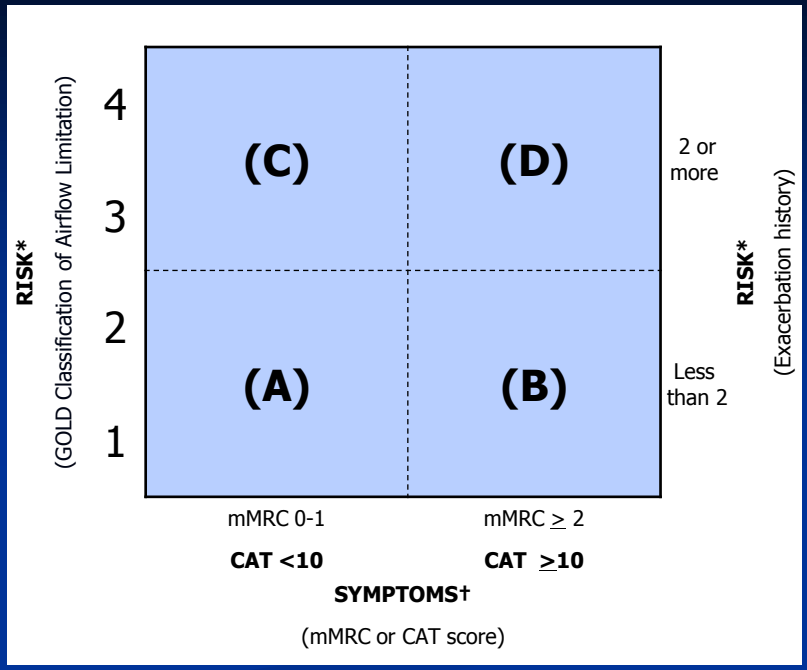


- Tiotropium group
  - Exacerbation risk was not modified by polymorphisms

2006


I: Mild
II: Moderate
III: Severe
IV: Very Severe
FEV1/FVC < 70%
FEV1 ≥ 80% pred.
FEV1/FVC < 70%
50% ≤ FEV1 < 80% predicted
FEV1/FVC < 70%
30% ≤ FEV1 < 50% predicted
FEV1/FVC < 70%
FEV1 < 30% pred.
FEV1 < 50% pred.
Plus Chronic respiratory failure
Active reduction of risk factor(s); influenza vaccination
Add short-acting bronchodilator (when needed)
Add regular treatment with one or more long-acting bronchodilators (when needed); Add rehabilitation
Add inhaled glucocorticosteroids if repeated exacerbations
Add long term oxygen if chronic respiratory failure. Consider surgical treatments

2011


RISK*
(GOLD Classification of Airflow Limitation)
4
3
2
1
(C)
(D)
(A)
(B)
2 or more
Less than 2
RISK*
(Exacerbation history)
mMRC 0-1
CAT <10
mMRC ≥ 2
CAT ≥10
SYMPTOMS†
(mMRC or CAT score)


ONE-SIZE FITS ALL STORE
SALE
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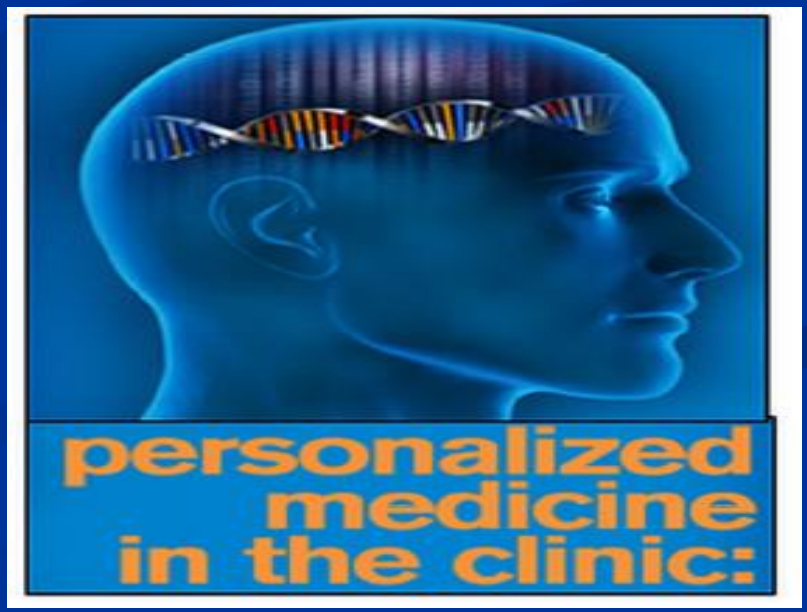

personalized medicine in the clinic:

Conclusion

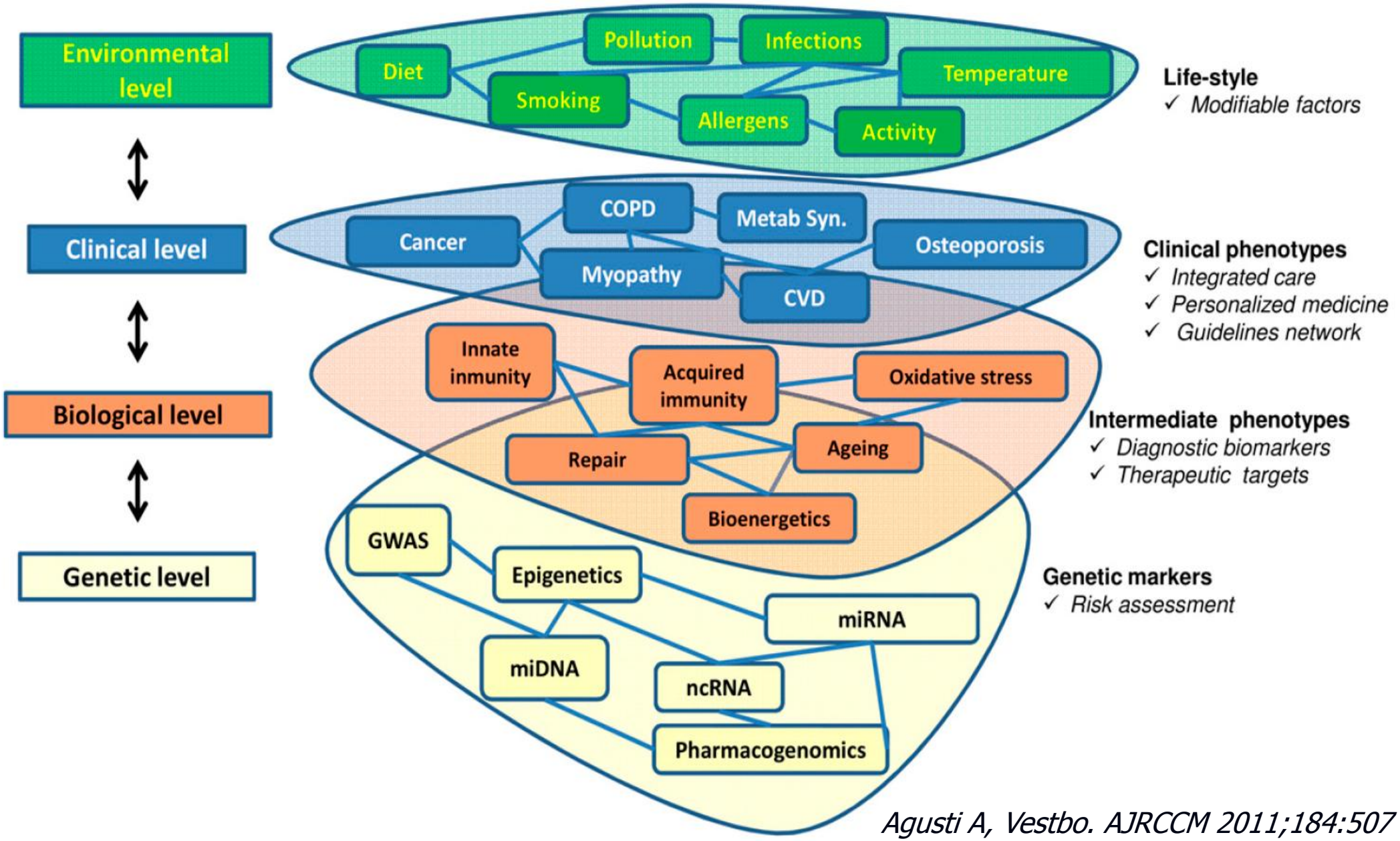
- Understanding of COPD has changed dramatically over the past two decades
  - Airflow limitation centric view (FEV_1)
  - complex and heterogenous disease

- COPD phenotypes are the basis of personalized treatment in clinical practice

- Clinical, inflammatory, genomic and epigenomic biomarkers for COPD could be used to personalize treatment

Control Panel Fulfilling Goal of 'Personalized' Medicine in COPD

Personalized Treatment in COPD



Agusti A, Vestbo. AJRCCM 2011;184:507