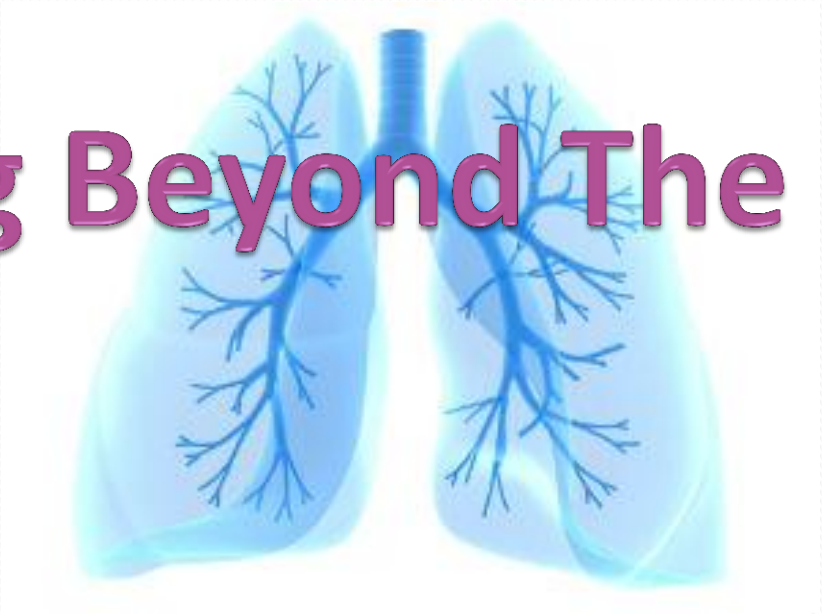
Going Beyond The Lungs

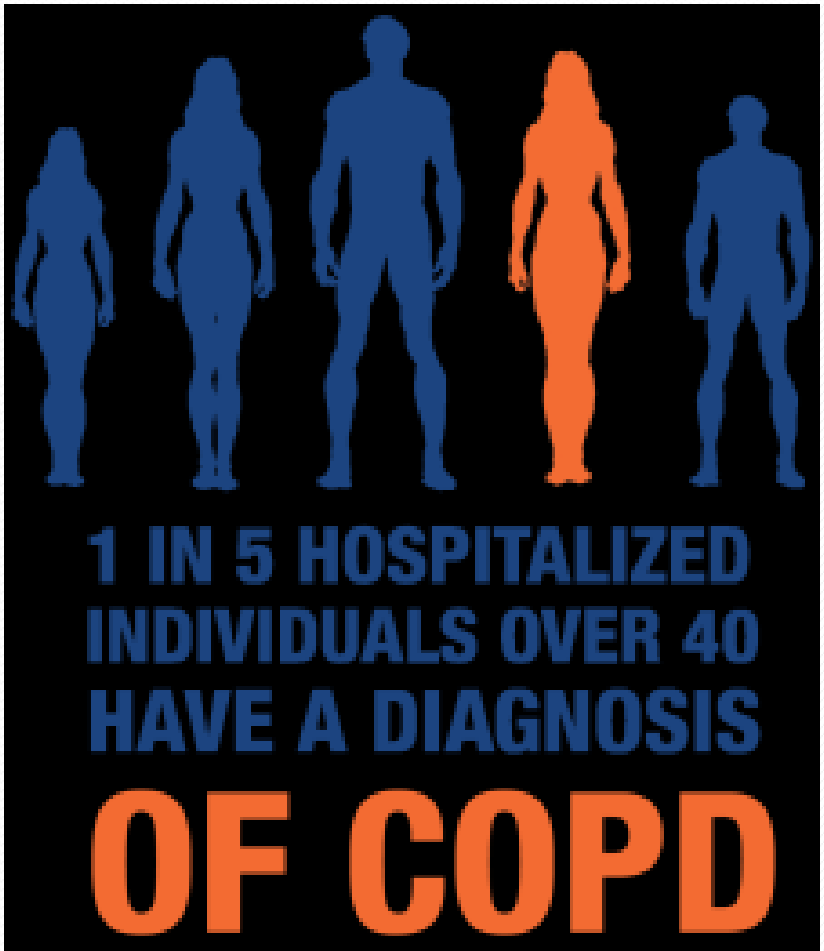


Prof: Win Naing
Prof:/ Head
Dept: of Respiratory Medicine
UM(1)/ YSH

Disclosure

I have no actual or potential conflict of interest in relation to this presentation.

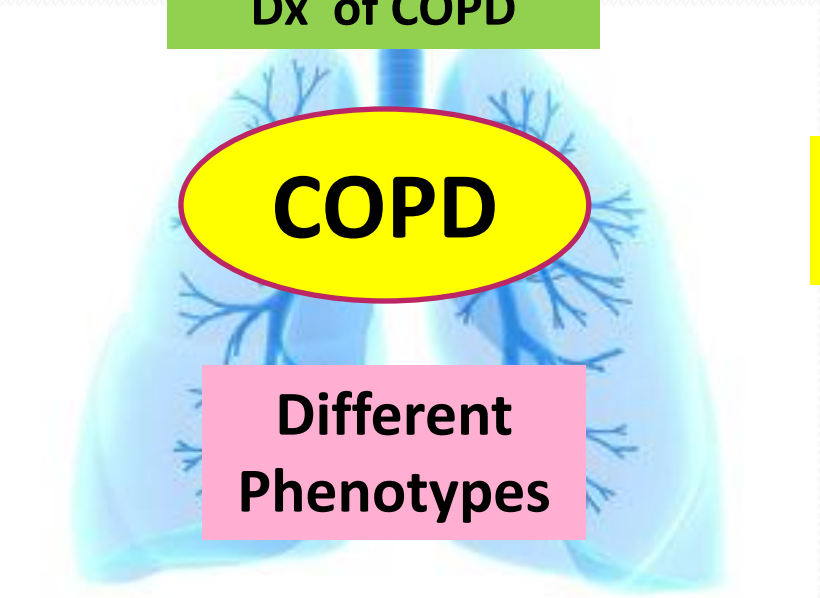
COPD is predicted to become the third leading cause of global mortality by 2020.



- The prevalence of COPD ?
- Under diagnosis as the symptoms may only become apparent only after a considerable loss of lung function
- Spirometry may not be readily available

Assessment of COPD

Dx of COPD



Different causes

Extrapulmonary systemic effects

Diversity of counter measures

Different Phenotypes

Different drugs with pros & cons

Different therapeutic agents

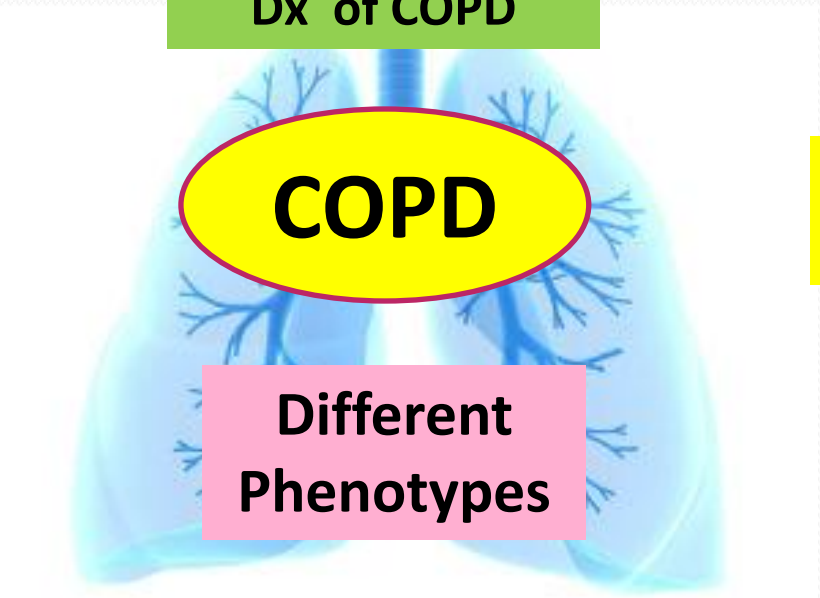
Common strategy & drugs

Genetics

Environments

Assessment of COPD

Dx of COPD



Different causes

Extrapulmonary systemic effects

Diversity of counter measures

Different Phenotypes

Different drugs with pros & cons

Different therapeutic agents

Common strategy & drugs

Genetics

Environments

COPD

COPD is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and **airflow limitation** that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

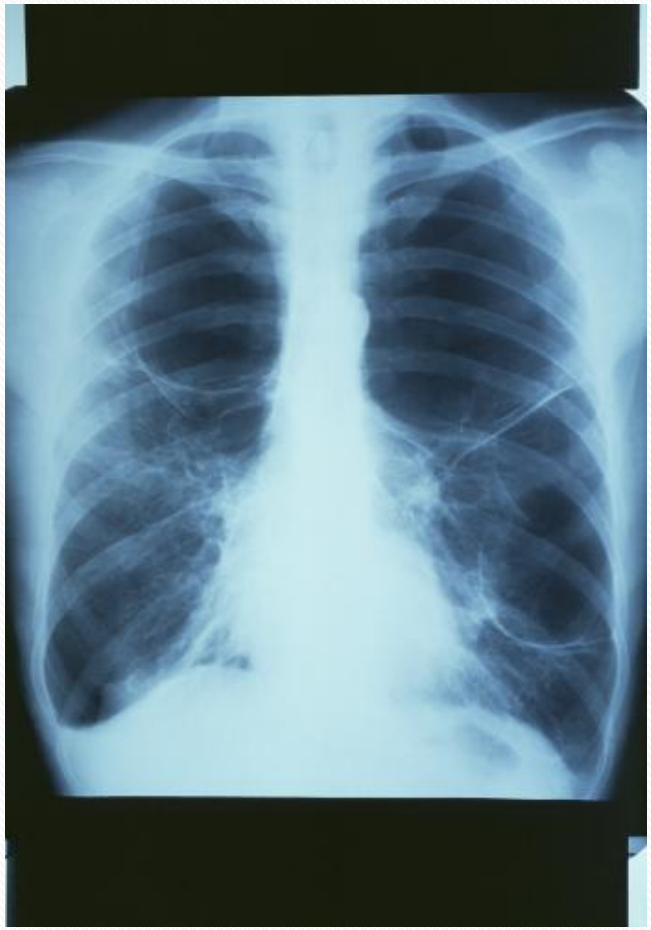
GOLD 2017

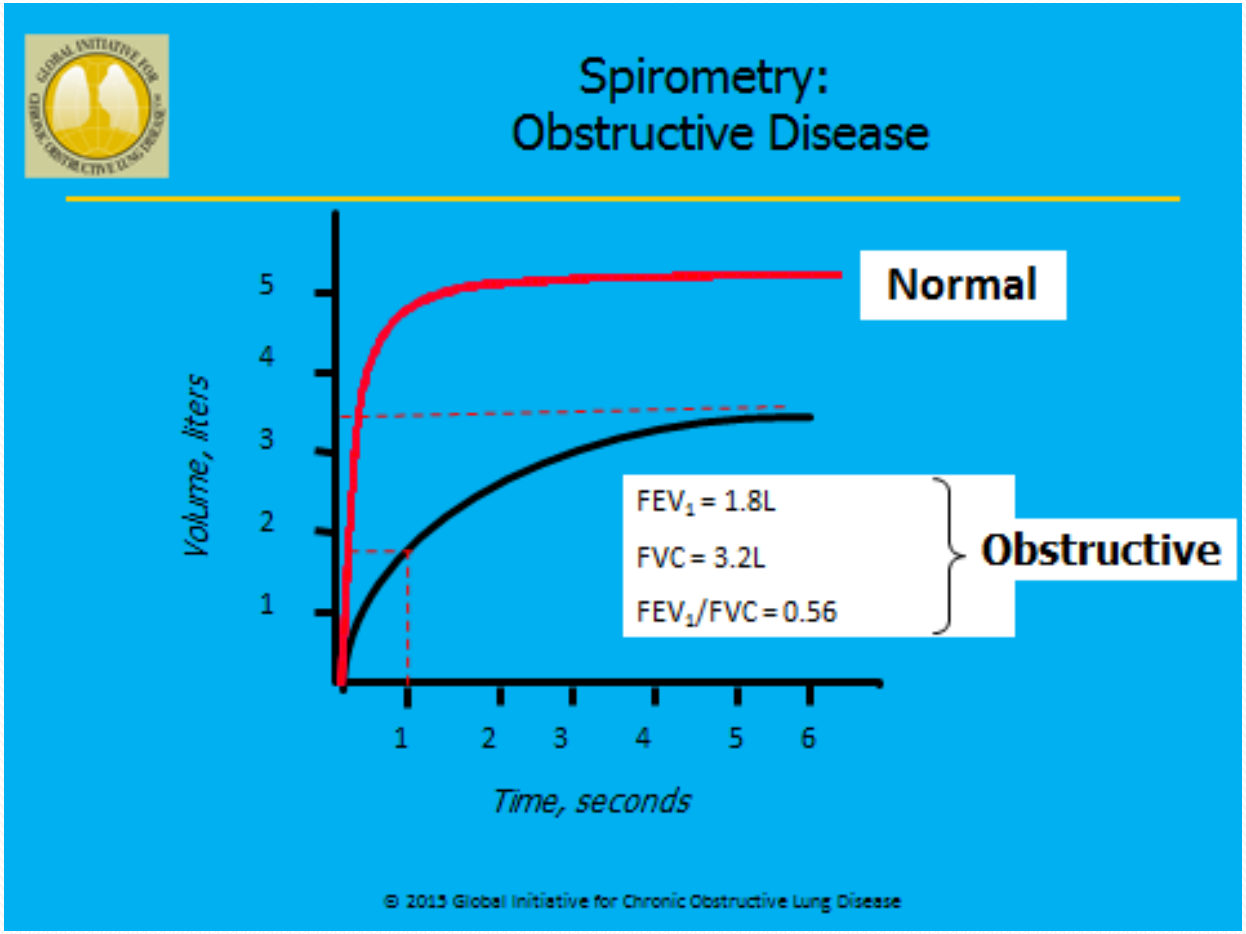
Dx of COPD

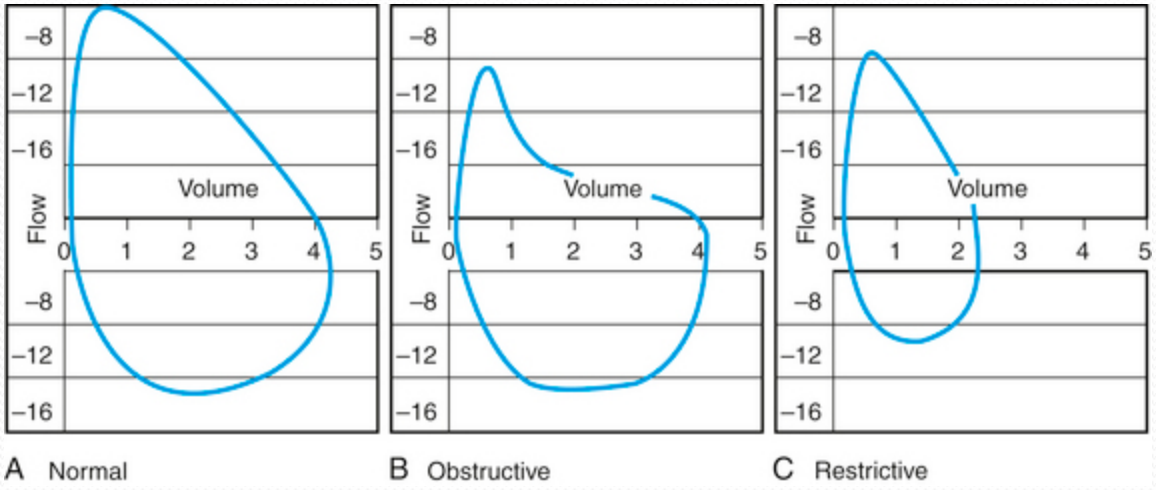
COPD

- COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or history of exposure to risk factors for the disease.
- A detailed medical history of a new patient who is known, or suspected, to have COPD is essential.
- Spirometry is required to make the diagnosis in this clinical context.

GOLD 2017

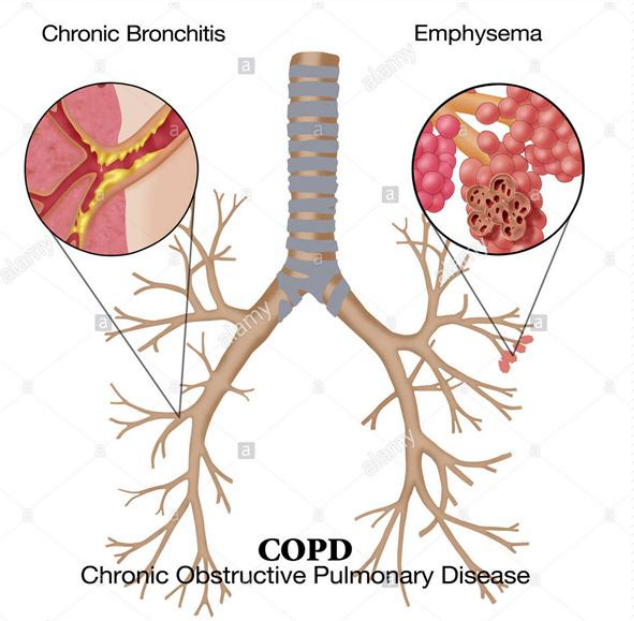


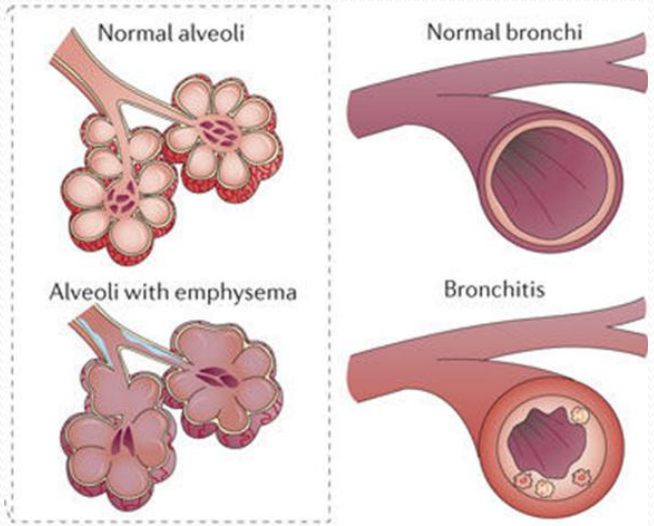

Spirometry:
Obstructive Disease
Normal
Obstructive
FEV1 = 1.8L
FVC = 3.2L
FEV1/FVC = 0.56
Volume, liters
Time, seconds
1
2
3
4
5
6
© 2015 Global Initiative for Chronic Obstructive Lung Disease



Flow – volume loops

- The chronic airflow limitation that is characteristic of COPD is caused by a mixture of small airways disease (e.g., obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which **vary from person to person**





GOLD 2017

Assessment of COPD

Dx of COPD

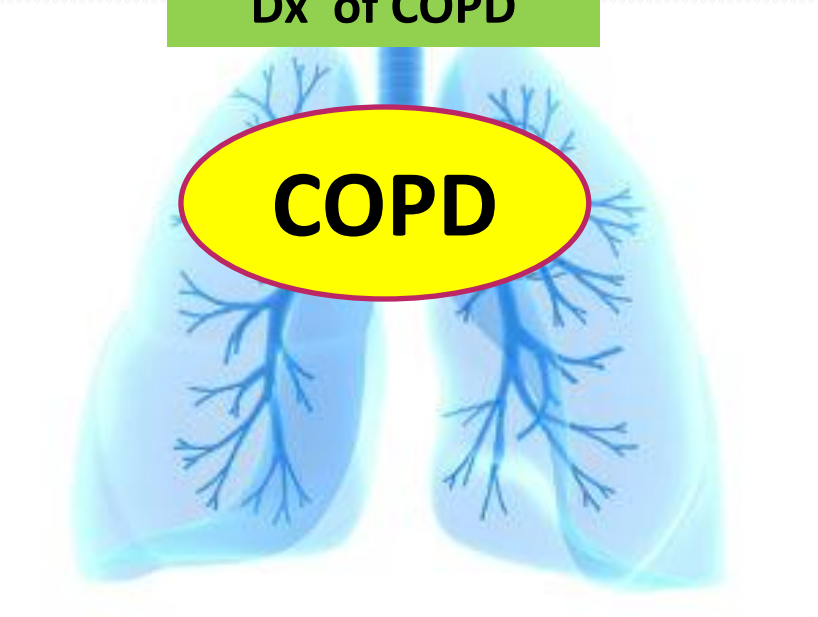
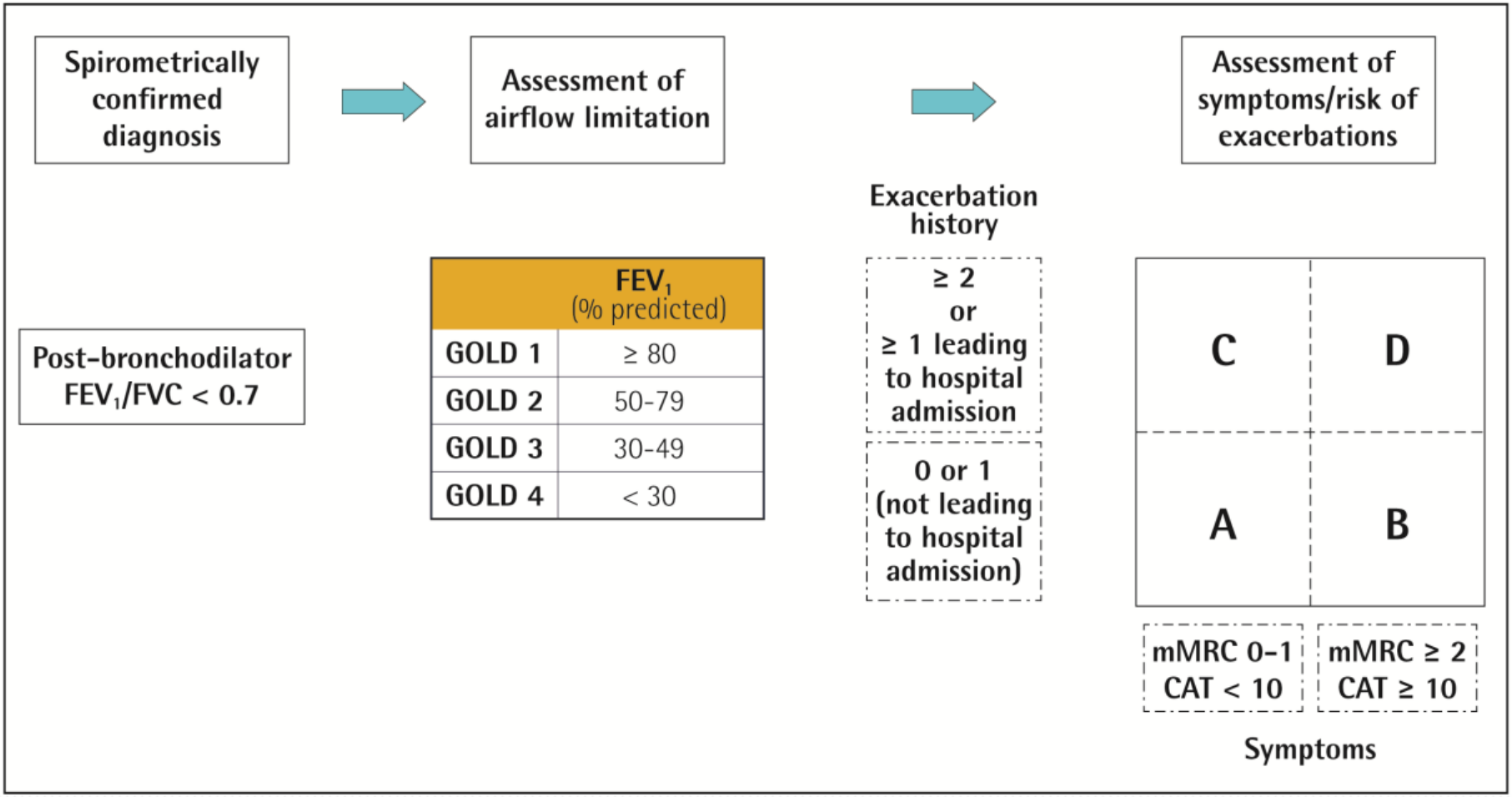


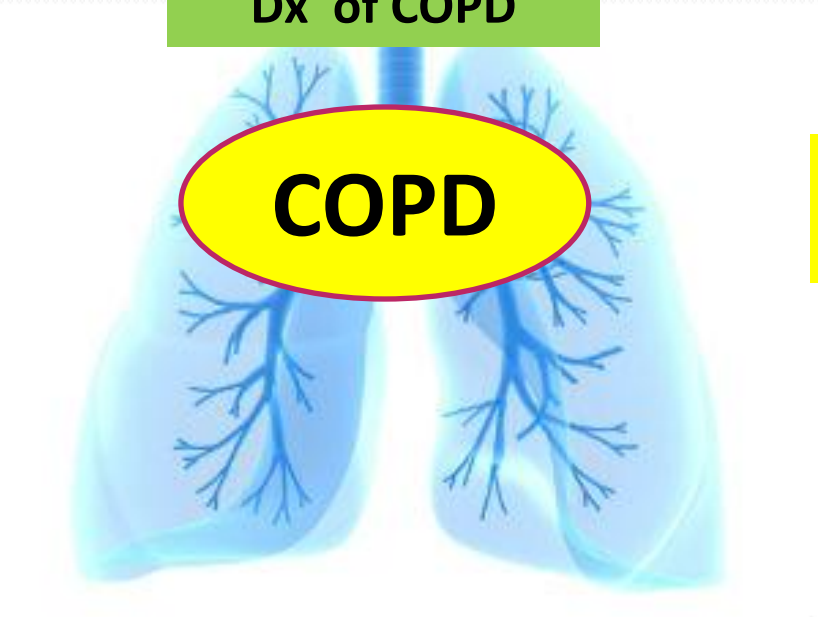
Figure 2.4. The refined ABCD assessment tool



GOLD 2017

Assessment of COPD

Dx of COPD

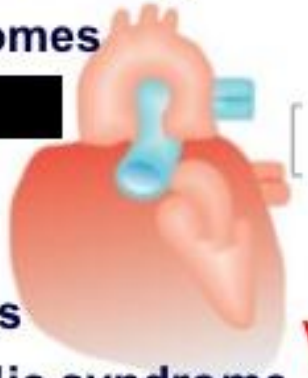


Extrapulmonary systemic effects

Systemic Effects of COPD

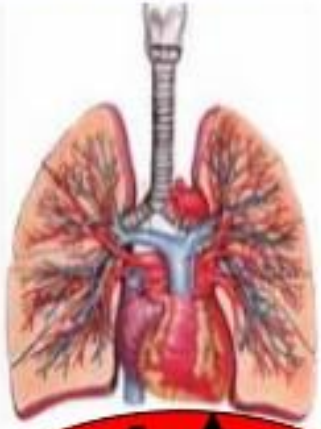
Angina

Acute coronary syndromes



Lung Infections

Lung Cancer

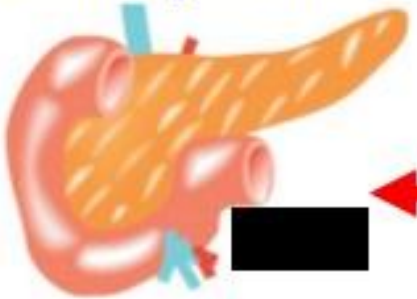


Weight loss

Muscle weakness

Diabetes

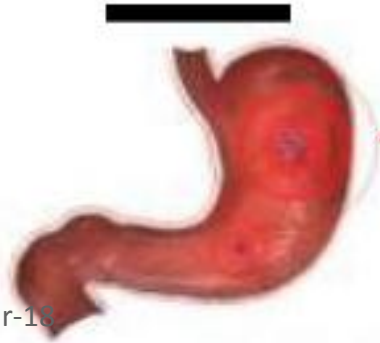
Metabolic syndrome



Osteoporosis

Systemic Inflammation Oxidatitive Stress

Peptic ulceration

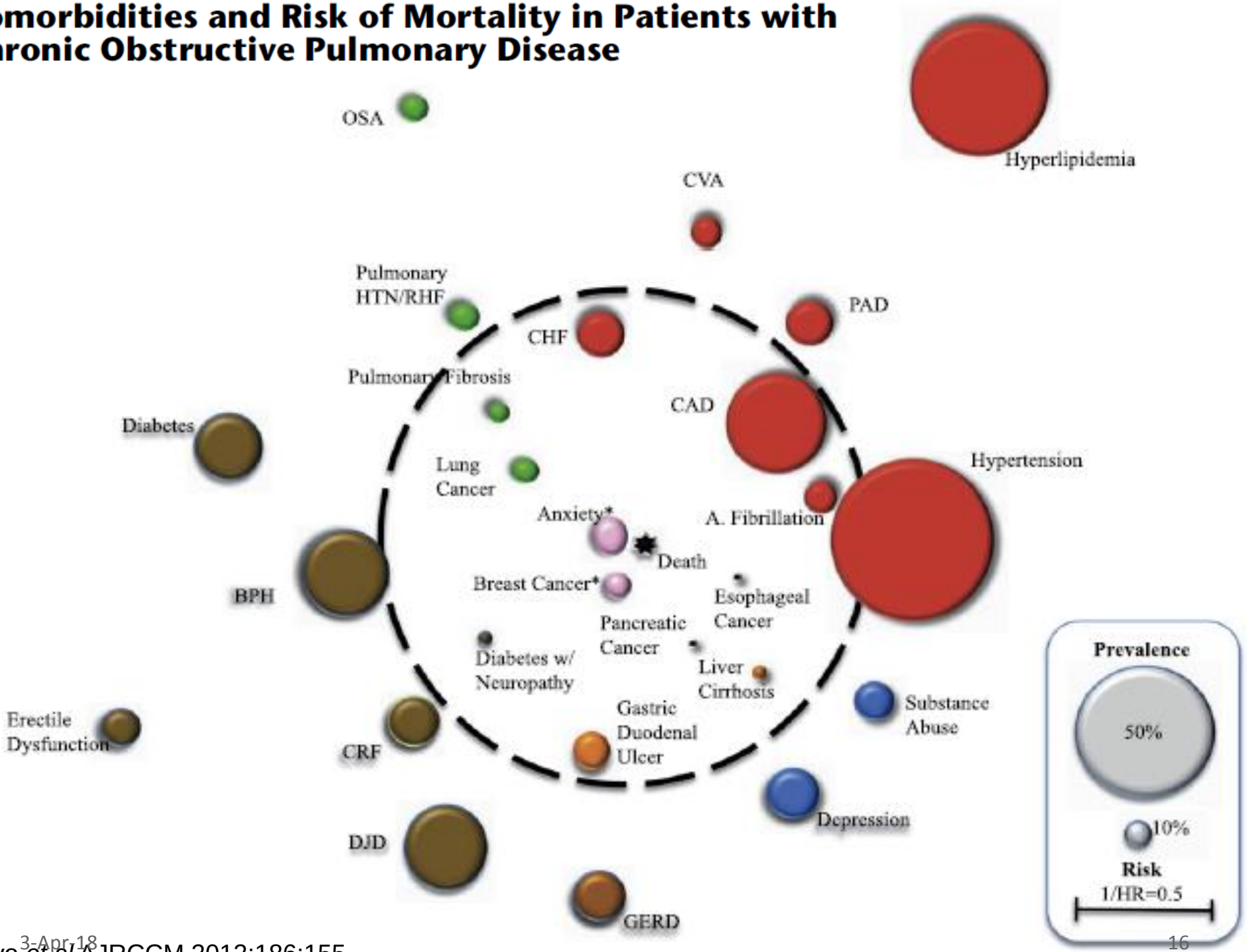


Depression

Depression

Fabbri, ERJ, 2008

Comorbidities and Risk of Mortality in Patients with Chronic Obstructive Pulmonary Disease

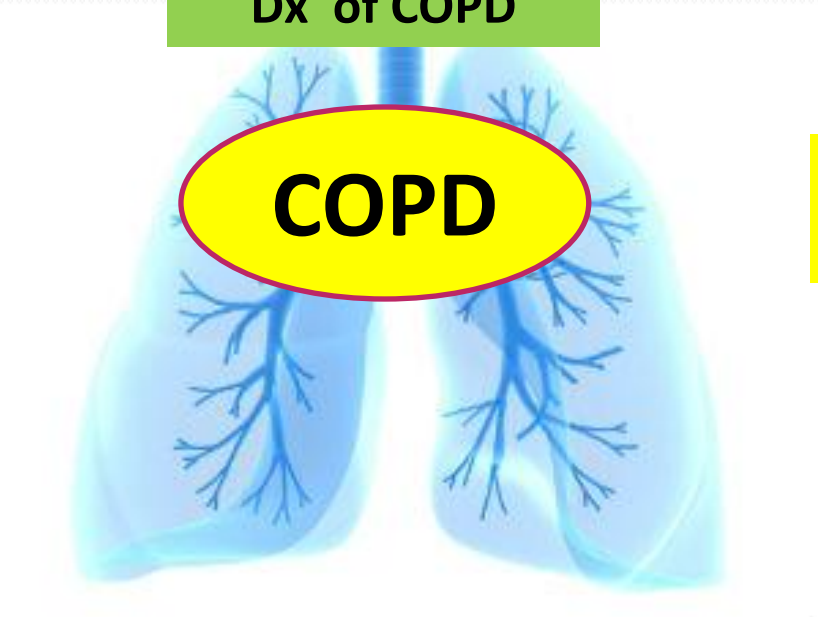


Divo *et al* AJRCCM 2012;186:155

Assessment of COPD

Dx of COPD

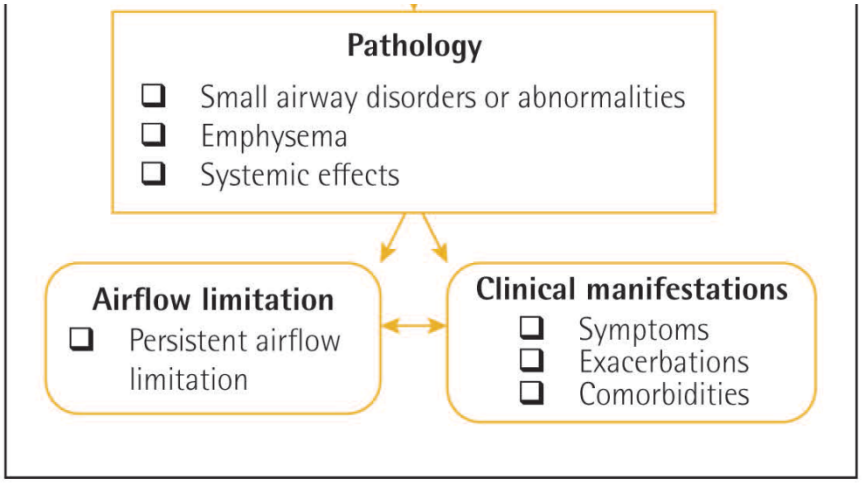
Different causes



Extrapulmonary systemic effects

Figure 1.1. Etiology, pathobiology and pathology of COPD leading to airflow limitation and clinical manifestations

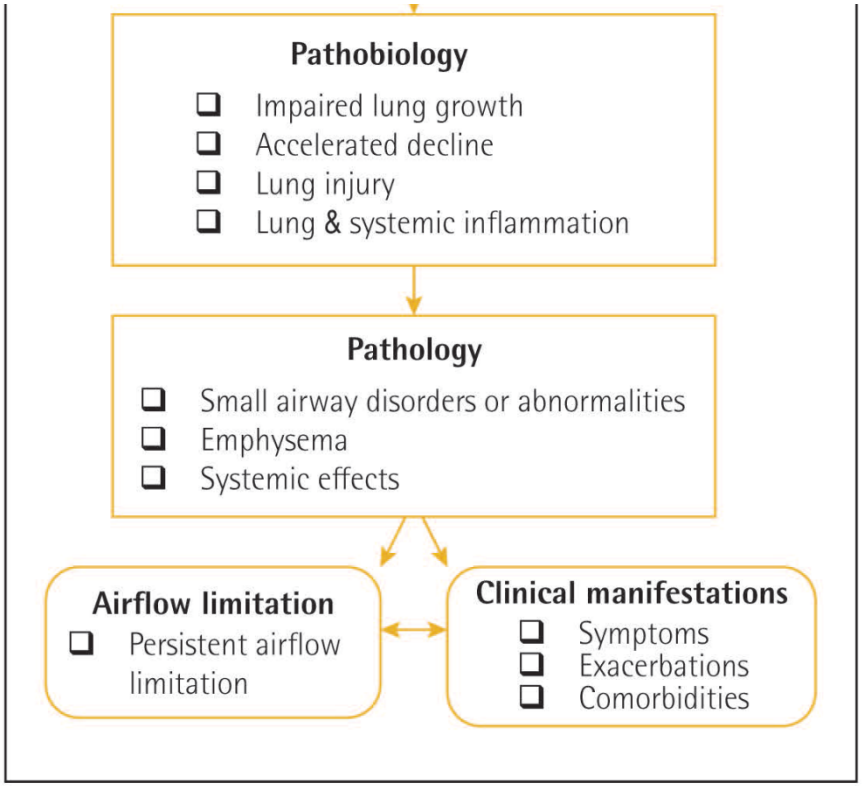
COPD



GOLD 2017

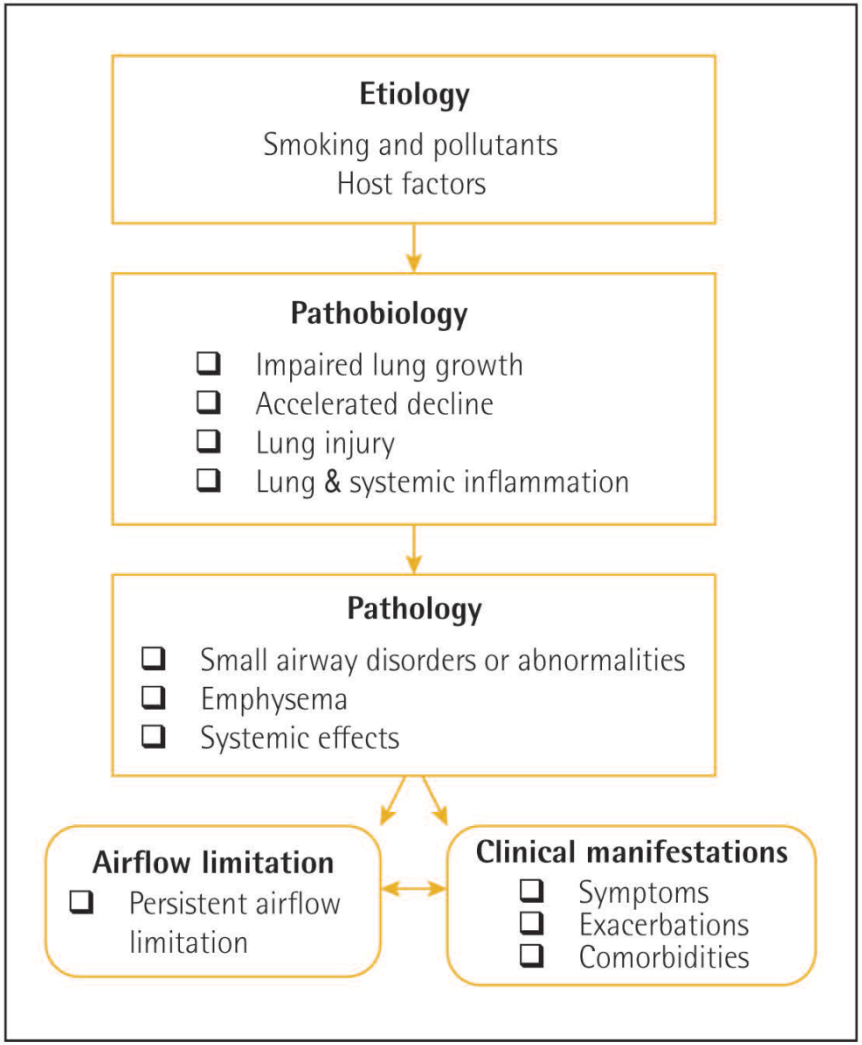
Figure 1.1. Etiology, pathobiology and pathology of COPD leading to airflow limitation and clinical manifestations

COPD

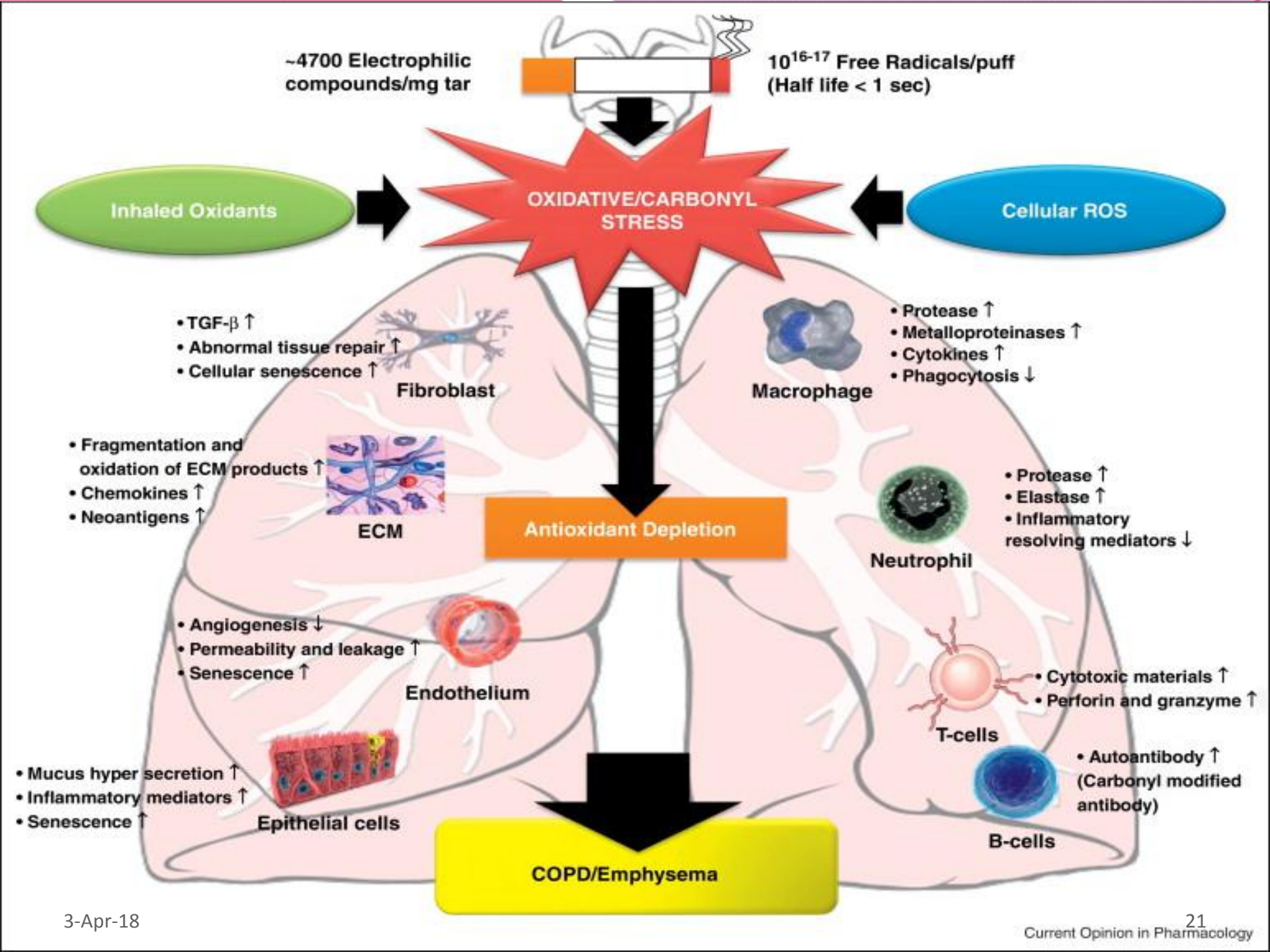


GOLD 2017

Figure 1.1. Etiology, pathobiology and pathology of COPD leading to airflow limitation and clinical manifestations



GOLD 2017

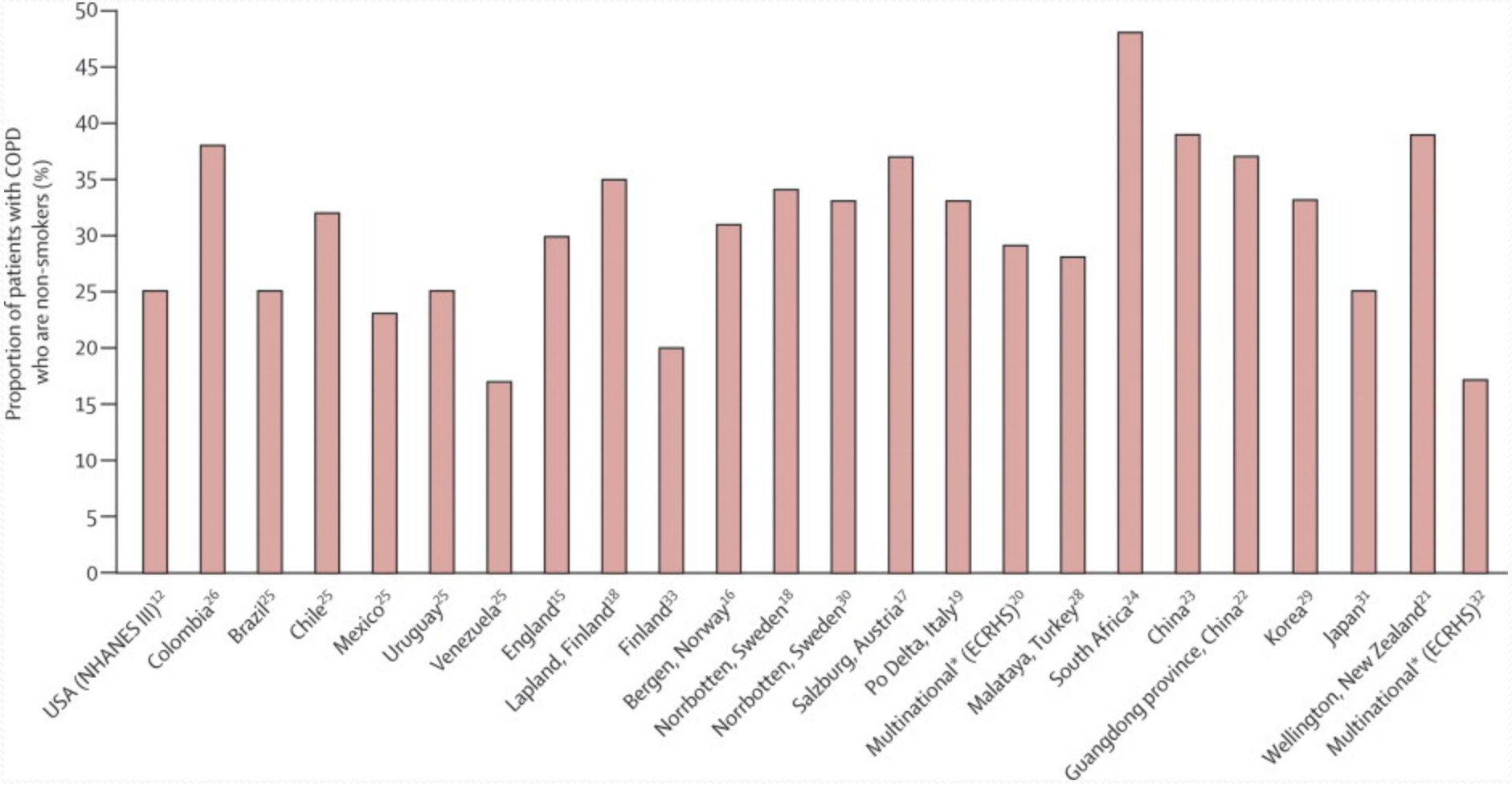


Current Opinion in Pharmacology

- Tobacco smoking is a major aetiological factor in the development of COPD.
- The association between cigarette smoking, accelerated loss of lung function and COPD is well established
- But, not all smokers go on to develop airflow obstruction

20% of COPD is not smoking-related

Proportion of non smoker COPD



Risk factors for development of COPD

- **Environmental**
- Tobacco smoke
- Indoor air pollution; cooking with biomass fuels
- Occupational exposures, such as coal dust, silica and cadmium
- Low birth weight
- Lung growth: childhood infections or maternal smoking
- Infections: recurrent infection / persistence of adenovirus /**HIV/TB**
- Low socioeconomic status
- Cannabis smoking
- **Host factors**
- Genetic factors: α1-antiproteinase deficiency
- Airway hyper-reactivity

Smoking

- is undoubtedly at the centre among other causes
- increases the risk of influenza & pneumonia & TB
- influences the progression & course of TB

COPD & TB

- Immunological mediators affecting the lung parenchyma
- Destruction of the pulmonary extra-cellular matrix (ECM) (structural integrity of lung)
- Increased expression of certain matrix metalloproteinases (MMPs)
- Re-modelling of the pulmonary ECM and structural changes in the lung

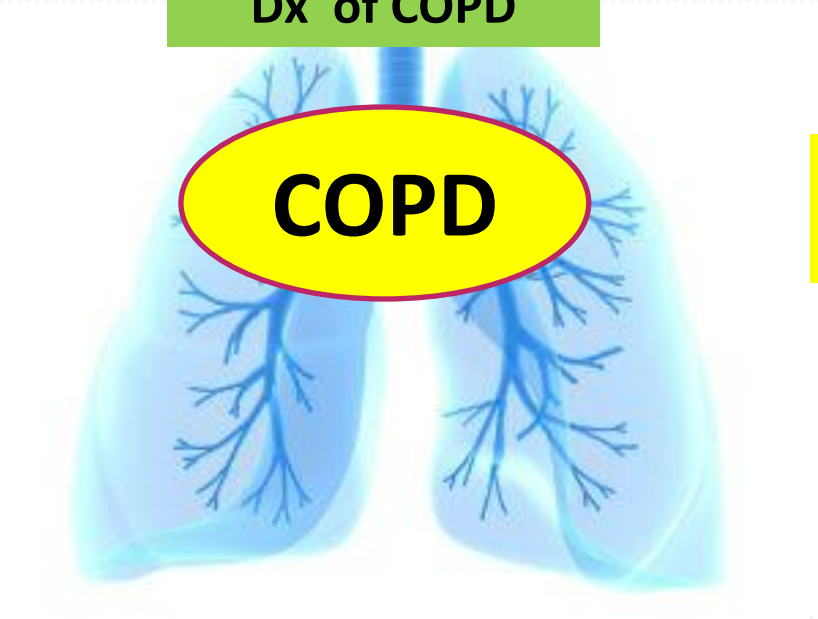
TB

- a significant public health problem both in developed & developing world
- A third of the world's population → LTBI
- 10% of LTBI will develop active TB during their lifetime

  (50% in the immuno-compromised)
- TB will remain 7th in leading cause of death and disability worldwide by 2020
- COPD is also predicted to become the third leading cause of global mortality by 2020

Assessment of COPD

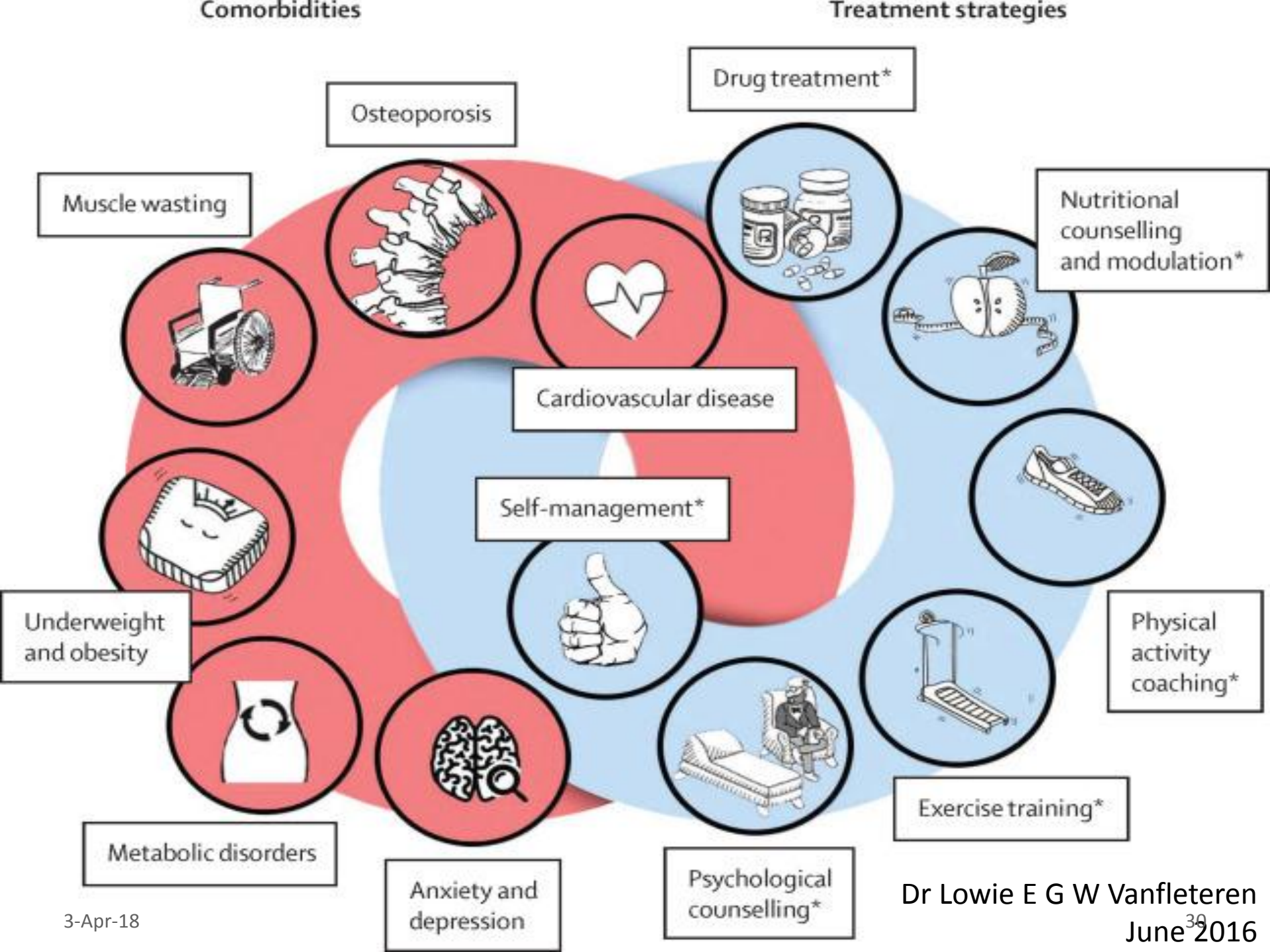
Dx of COPD



Different causes

Extrapulmonary systemic effects

Different drugs with pros & cons

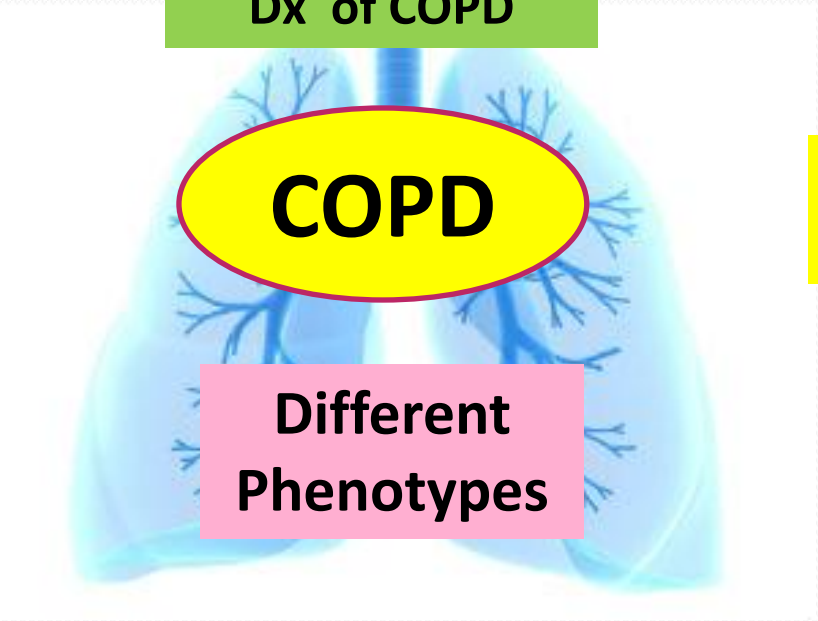


Dr Lowie E G W Vanfleteren
June 2016

- Systemic manifestations and comorbidities of COPD warrant an individualised approach as part of integrated disease management.
- When COPD is part of a multimorbidity care plan, attention should be directed
  - to ensure simplicity of treatment and
  - to minimize polypharmacy.

Assessment of COPD

Dx of COPD



Different causes

Extrapulmonary systemic effects

Different Phenotypes

Different drugs with pros & cons

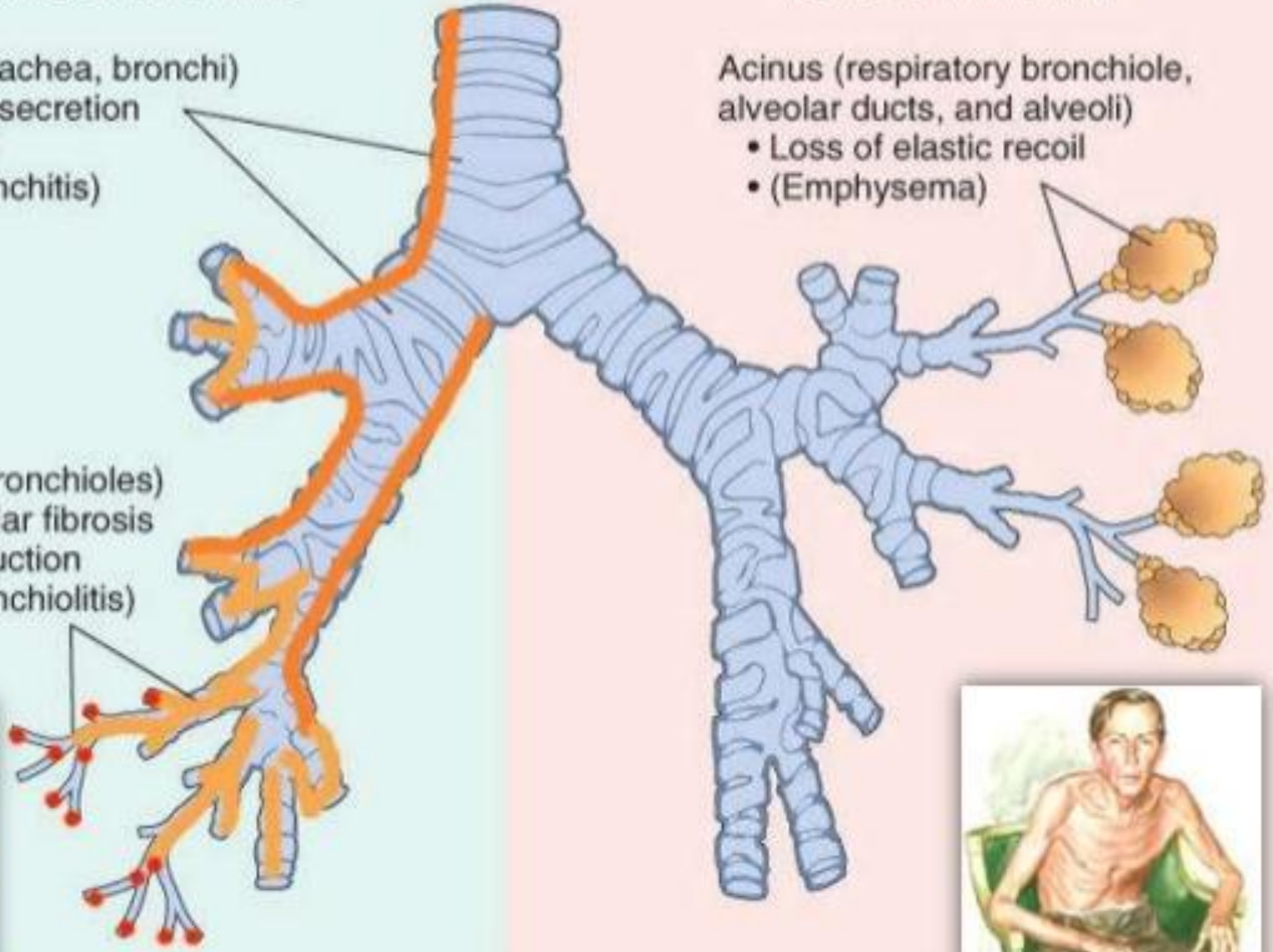
PURE CHRONIC BRONCHITIS

Large airways (trachea, bronchi)
- Mucus hypersecretion
- Inflammation
- (Chronic bronchitis)

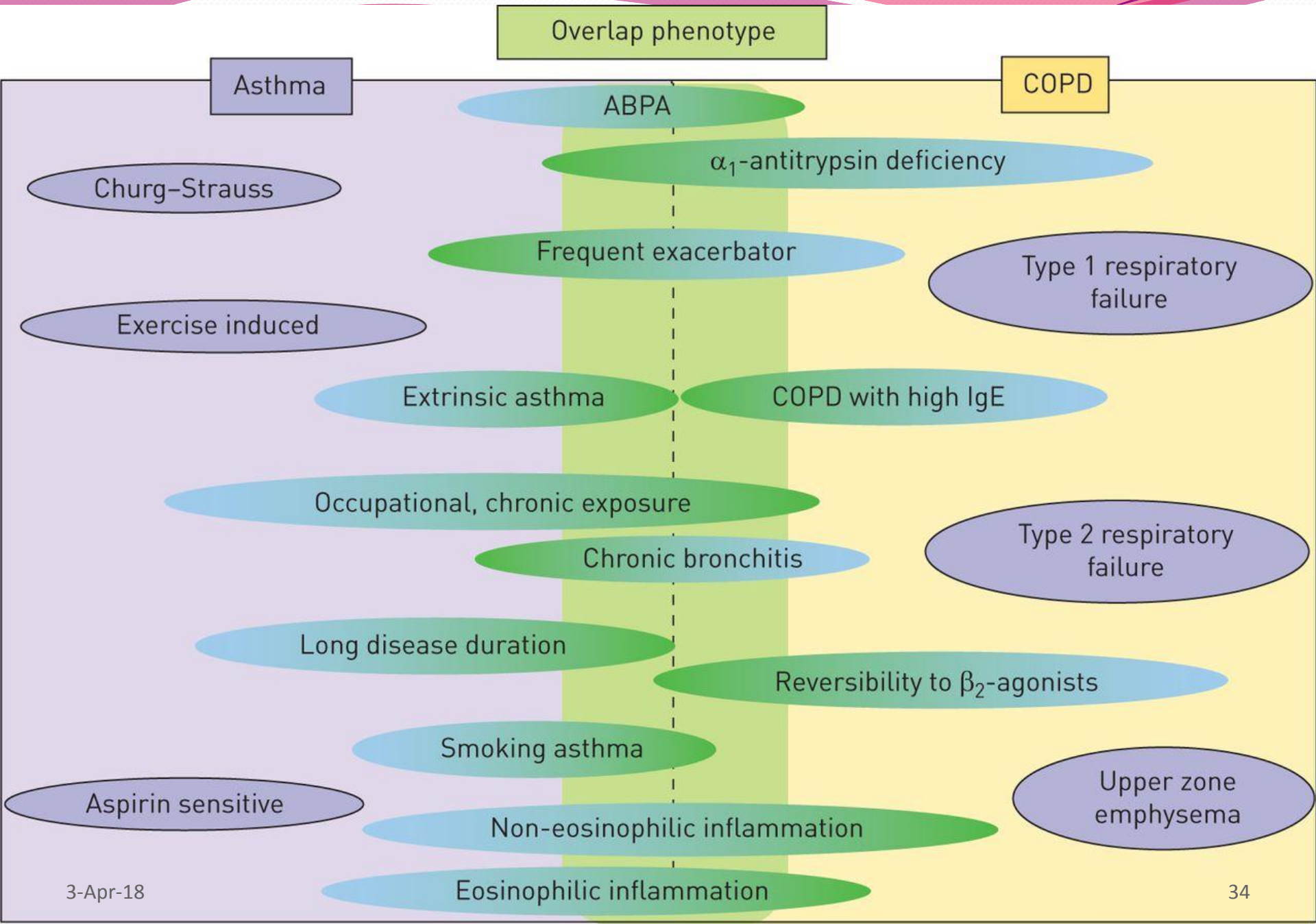
Small airways (bronchioles)
- Peribronchiolar fibrosis
- Airway obstruction
- (Chronic bronchiolitis)

PURE EMPHYSEMA

Acinus (respiratory bronchiole, alveolar ducts, and alveoli)
- Loss of elastic recoil
- (Emphysema)



Both affected commonly → COPD


Overlap phenotype
Asthma
COPD
ABPA
α1-antitrypsin deficiency
Churg–Strauss
Frequent exacerbator
Type 1 respiratory failure
Exercise induced
Extrinsic asthma
COPD with high IgE
Occupational, chronic exposure
Type 2 respiratory failure
Chronic bronchitis
Long disease duration
Reversibility to β2-agonists
Smoking asthma
Upper zone emphysema
Aspirin sensitive
Non-eosinophilic inflammation
Eosinophilic inflammation

COPD phenotypes

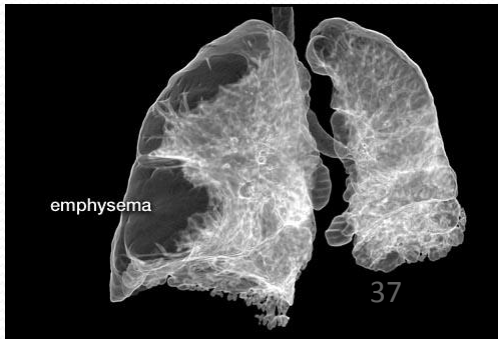
- The concept of a clinical COPD phenotype has been proposed as the goal of COPD phenotyping is to be able to classify patients into distinct **subgroups** according to prognosis and response to therapy in order to better select the appropriate therapy that can **optimize** clinically meaningful outcomes for patients.

Int J Chron Obstruct Pulmon Dis. 2016;

What phenotypes have been proposed?

- The ECLIPSE study → several COPD phenotypes & potential biomarkers for predicting clinical outcomes
- At least three COPD phenotypes have been validated
  1. **Alpha-1 antitrypsin deficiency**
  2. **Emphysema/ hyperinflation**
  3. **Frequent exacerbators**

- ***Alpha-1 antitrypsin deficiency*** → a genetic condition that predisposes to COPD and liver disease, and may respond positively to augmentation therapy
- ***Emphysema/ hyperinflation*** → upper-lobe emphysema, dyspnea, and poor exercise capacity, associated with severe airflow limitation & respond well to lung volume reduction surgery, which improves survival



- ***Frequent exacerbators*** (≥2 per year)→ have poor QOL, increased mortality, and a greater decline in lung function.
  - high risk for GERD
  - more severe airway obstruction, with significantly higher modified MRC dyspnea scale
  - increased (BODE) index

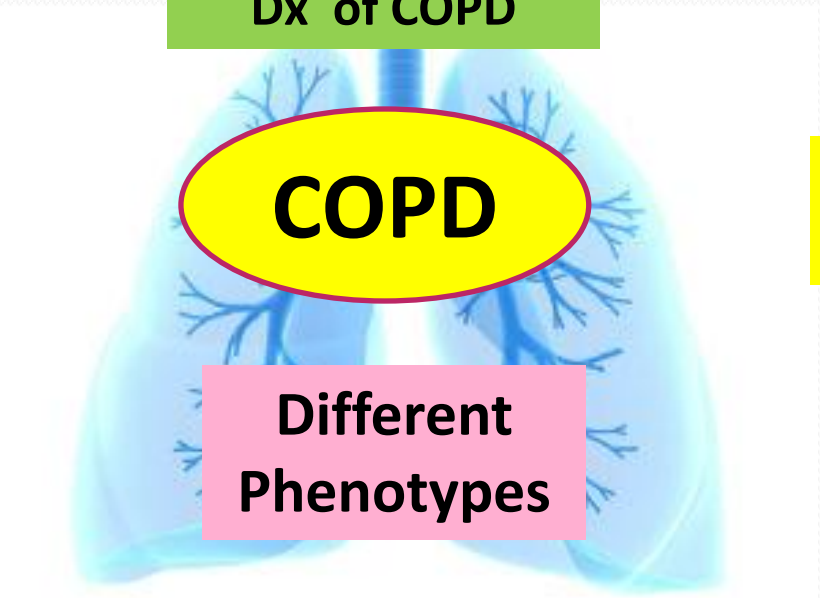
Other phenotypes proposed

- Mild airway obstruction but disproportionately severe dyspnea
- Rapid lung function decline
- Comorbidities
- Persistent inflammation, defined by ongoing elevation of blood inflammatory markers such as CRP, fibrinogen,WBC
- Chronic bacterial airway colonization
- Lung cancer phenotype
- Severe pulmonary hypertension
- Non-smokers
- Overlap of symptoms between asthma and COPD

Assessment of COPD

Dx of COPD

Different causes



Extrapulmonary systemic effects

Different Phenotypes

Different drugs with pros & cons

Different therapeutic agents

I : Mild	II : Moderate	III : Severe	IV : Very severe
• $FEV_1/FVC < 0.70$ • $FEV_1 \geq 80\%$ predicted	• $FEV_1/FVC < 0.70$ • $50\% \leq FEV_1 < 80\%$ predicted	• $FEV_1/FVC < 0.70$ • $30\% \leq FEV_1 < 50\%$ predicted	• $FEV_1/FVC < 0.70$ • $FEV_1 < 30\%$ predicted *or* $FEV_1 < 50\%$ predicted *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

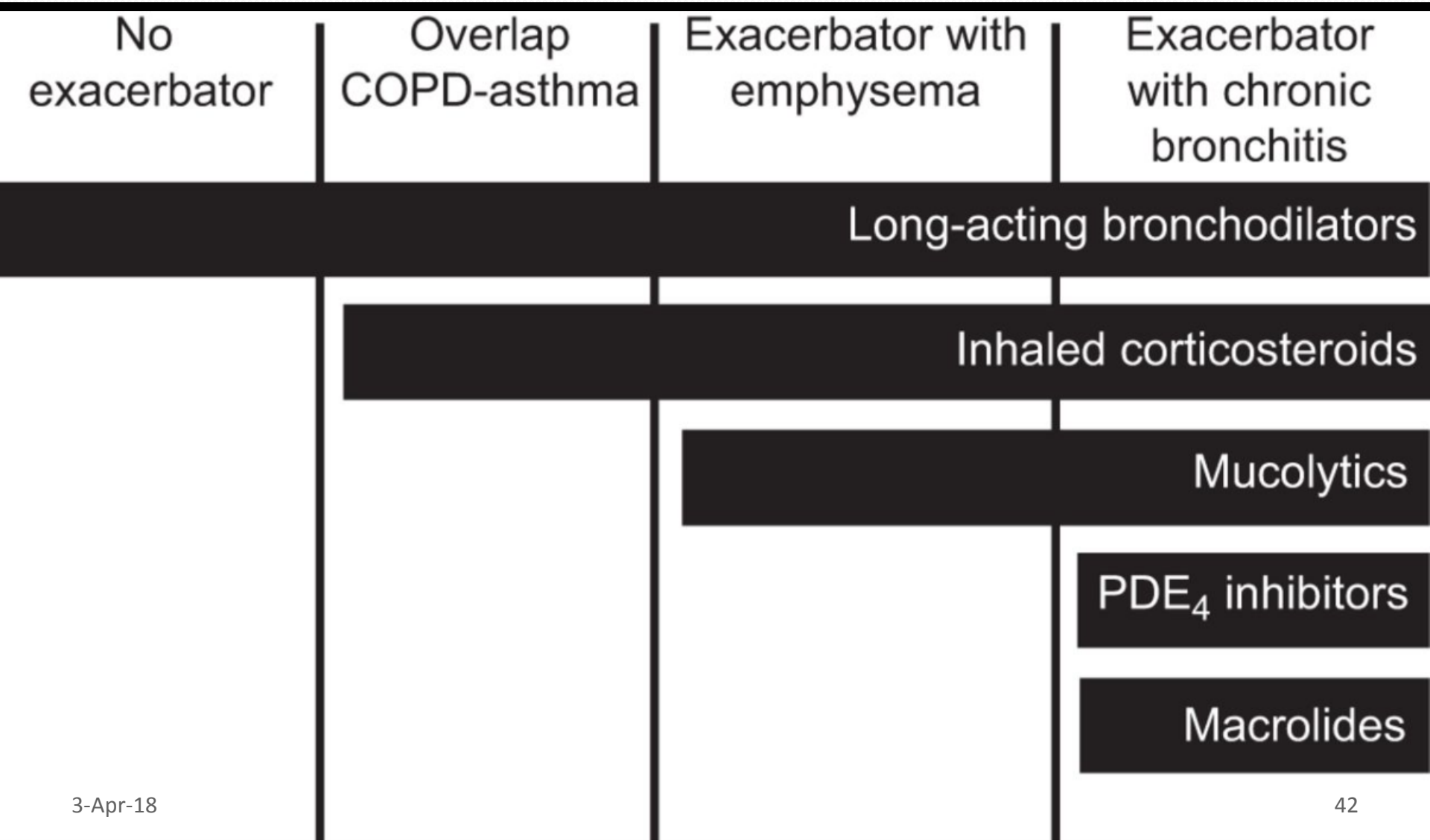
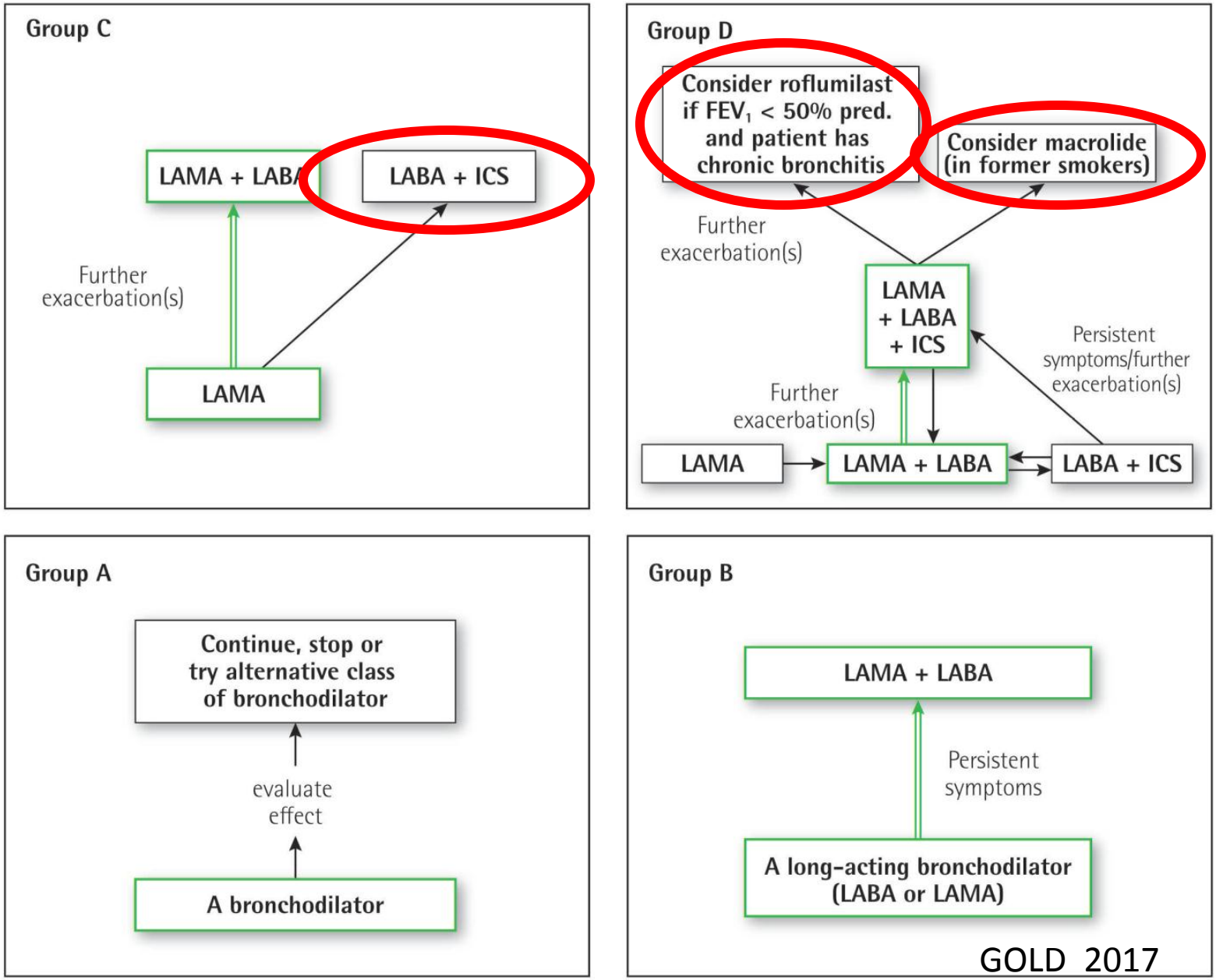

No exacerbator
Overlap COPD-asthma
Exacerbator with emphysema
Exacerbator with chronic bronchitis
Long-acting bronchodilators
Inhaled corticosteroids
Mucolytics
PDE4 inhibitors
Macrolides

Table 3.3. Commonly used maintenance medications in COPD*

Drug	Inhaler (mcg)	Solution for nebulizer (mg/ml)	Oral	Vials for injection (mg)	Duration of action (hours)
Beta$_2$-agonists					
Short-acting					
Fenoterol	100-200 (MDI)	1	2.5 mg (pill), 0.05% (syrup)		4-6
Levalbuterol	45-90 (MDI)	0.1, 0.21, 0.25, 0.42			6-8
Salbutamol (albuterol)	90, 100, 200 (MDI & DPI)†	1, 2, 2.5, 5 mg/ml	2, 4, 5 mg (pill)	0.1, 0.5 mg	4, 6, 12 (ex
Terbutaline					
Long-acting					
Arformoterol					
Formoterol					
Indacaterol					
Olodaterol					
Salmeterol					
Anticholinergics					
Short-acting					
Ipratropium bromide	20, 40 (MDI)	0.2			6-8
Oxitropium bromide	100 (MDI)				7-9
Long-acting					
Aclidinium bromide	400 (DPI), 400 (MDI)				12
Glycopyrronium bromide	15.6 & 50 (DPI)†		1 mg (solution)	0.2 mg	12-24
Tiotropium	18 (DPI), 2.5 & 5 (SMI)				24
Umeclidinium	62.5 (DPI)				24
Combination of sh					
Fenoterol/ipratropiu					
Salbutamol/ipratropi					
Combination of lo					
Formoterol/aclidiniu					
Formoterol/glycopyr					
Indacaterol/glycopyr					
Vilanterol/umeclidin					
Olodaterol/tiotropiu					
Methylxanthines					
Aminophylline			105 mg/ml (solution)	250, 500 mg	Variable, up to 24
Theophylline (SR)			100-600 mg (pill)	250, 400, 500 mg	Variable, up to 24
Combination of long-acting beta$_2$-agonist plus corticosteroids in one device					
Formoterol/ beclomethasone	6/100 (MDI & DPI)				
Formoterol/budesonide	4.5/160 (MDI), 4.5/80 (MDI), 9/320 (DPI), 9/160 (DPI)				
Formoterol/mometasone	10/200, 10/400 (MDI)				
Salmeterol/fluticasone	5/100, 50/250, 5/500 (DPI), 21/45, 21/115, 21/230 (MDI)				
Vilanterol/fluticasone furoate	25/100 (DPI)				
Phosphodiesterase-4 inhibitors					

GOLD 2017

Figure 4.1. Pharmacologic treatment algorithms by GOLD Grade [highlighted boxes and arrows indicate preferred treatment pathways]



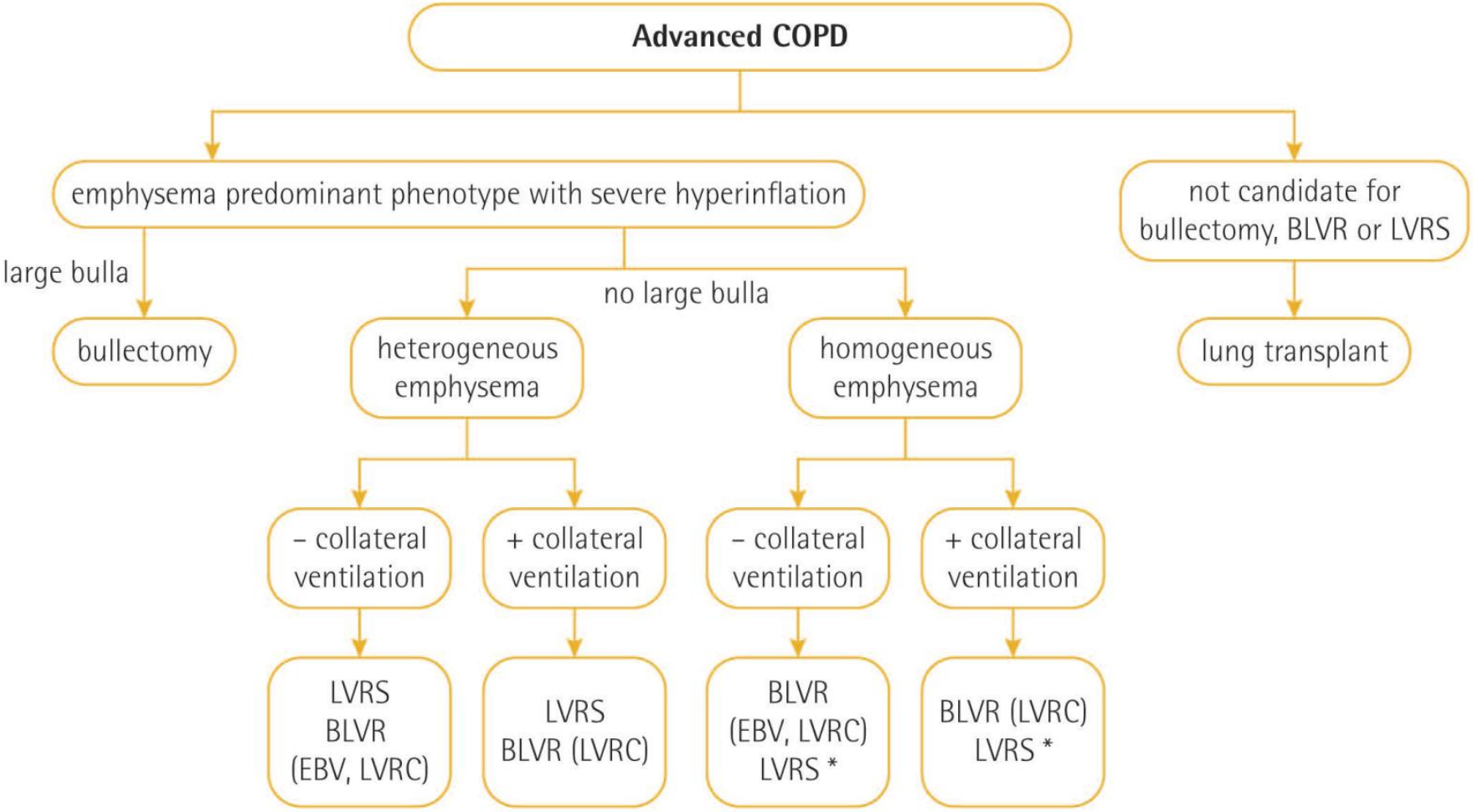
GOLD 2017

Preferred treatment =

In patients with a major discrepancy between the perceived level of symptoms and severity of airflow limitation, further evaluation is warranted.

Figure 4.3. Interventional Bronchoscopic and Surgical Treatments for COPD

Overview of various therapies used to treat patients with COPD and emphysema worldwide. Note that all therapies are not approved for clinical care in all countries. Additionally, the effects of BLVR on survival or other long term outcomes or comparison to LVRS are unknown.



Definition of Abbreviations: BLVR, Bronchoscopic Lung Volume Reduction, EBV, endobronchial Valve, LVRS, Lung volume reduction surgery, LVRC, Lung volume reduction coil

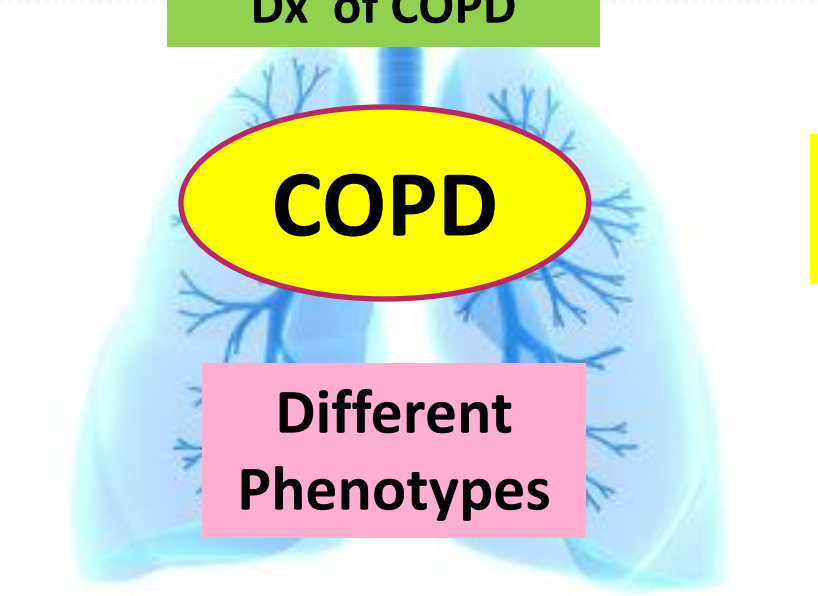
*at some but not all centers

GOLD 2017

Assessment of COPD

Dx of COPD

Different causes



Extrapulmonary systemic effects

Different drugs with pros & cons

Different therapeutic agents

Common strategy & drugs

American Thoracic Society Documents

American Thoracic Society/European Respiratory Society Statement on Pulmonary Rehabilitation

Linda Nici, Claudio Donner, Emiel Wouters, Richard Zuwallack, Nicolino Ambrosino, Jean Bourbeau, Mauro Carone, Bartolome Celli, Marielle Engelen, Bonnie Fahy, Chris Garvey, Roger Goldstein, Rik Gosselink Suzanne Lareau, Neil MacIntyre, Francois Maltais, Mike Morgan, Denis O'Donnell, Christian Prefault, Jane Reardon, Carolyn Rochester, Annemie Schols, Sally Singh, and Thierry Troosters, on behalf of the ATS/ERS Pulmonary Rehabilitation Writing Committee

CHEST

Official publication of the American College of Chest Physicians

CHEST ONLINE

Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines

Andrew L. Ries, Gerene S. Bauldoff, Brian W. Carlin, Richard Casaburi, Charles F. Emery, Donald A. Mahler, Barry Make, Carolyn L. Rochester, Richard ZuWallack and Carla Herrerias

Chest 2007;131:4-42
DOI 10.1378/chest.06-2418

Table 3.8. Pulmonary rehabilitation, self-management and integrative care in COPD

Pulmonary rehabilitation

- Pulmonary rehabilitation improves dyspnea, health status and exercise tolerance in stable patients **(Evidence A)**.
- Pulmonary rehabilitation reduces hospitalizations among patients who have had a recent exacerbation (≤ 4 weeks from prior hospitalization) **(Evidence B)**.

Education and self-management

- Education alone has not been shown to be effective **(Evidence C)**.
- Self-management intervention with communication with a health care professional improves health status and decreases hospitalizations and emergency department visits **(Evidence B)**.

Integrated care programs

- Integrated care and telehealth have no demonstrated benefit at this time **(Evidence B)**.

GOLD 2017

Table 3.10. Oxygen therapy and ventilatory support in stable COPD

Oxygen therapy

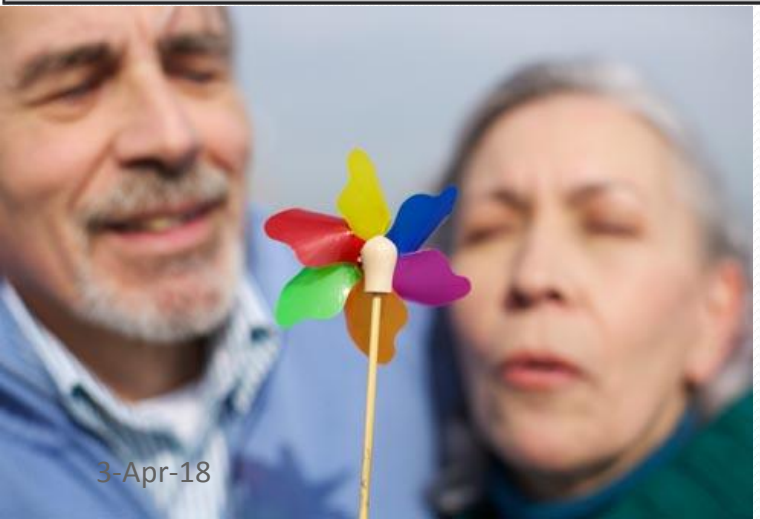
- The long-term administration of oxygen increases survival in patients with severe chronic resting arterial hypoxemia **(Evidence A)**.
- In patients with stable COPD and moderate resting or exercise-induced arterial desaturation, prescription of long-term oxygen does not lengthen time to death or first hospitalization or provide sustained benefit in health status, lung function and 6-minute walk distance **(Evidence A)**.
- Resting oxygenation at sea level does not exclude the development of severe hypoxemia when traveling by air **(Evidence C)**.

Ventilatory support

- NPPV may improve hospitalization-free survival in selected patients after recent hospitalization, particularly in those with pronounced daytime persistent hypercapnia ($PaCO_2 \geq 52$ mmHg) **(Evidence B)**.

GOLD 2017

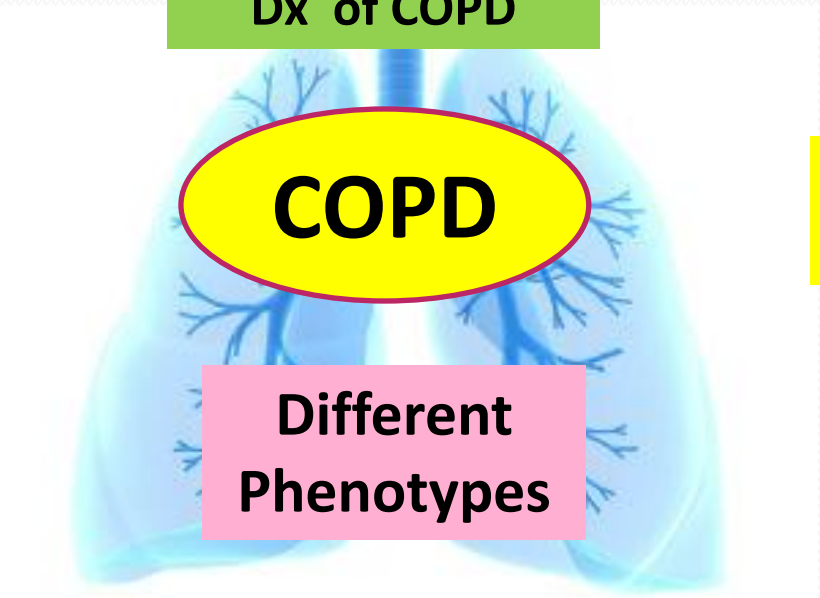
Table 4.8. Non-pharmacologic management of COPD			
Patient group	Essential	Recommended	Depending on local guidelines
A	Smoking cessation (can include pharmacologic treatment)	Physical activity	Flu vaccination Pneumococcal vaccination
B-D	Smoking cessation (can include pharmacologic treatment) Pulmonary rehabilitation	Physical activity	Flu vaccination Pneumococcal vaccination



GOLD 2017

Assessment of COPD

Dx of COPD



Different causes

Extrapulmonary systemic effects

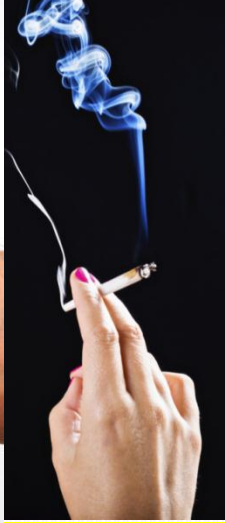
Diversity of counter measures

Different Phenotypes

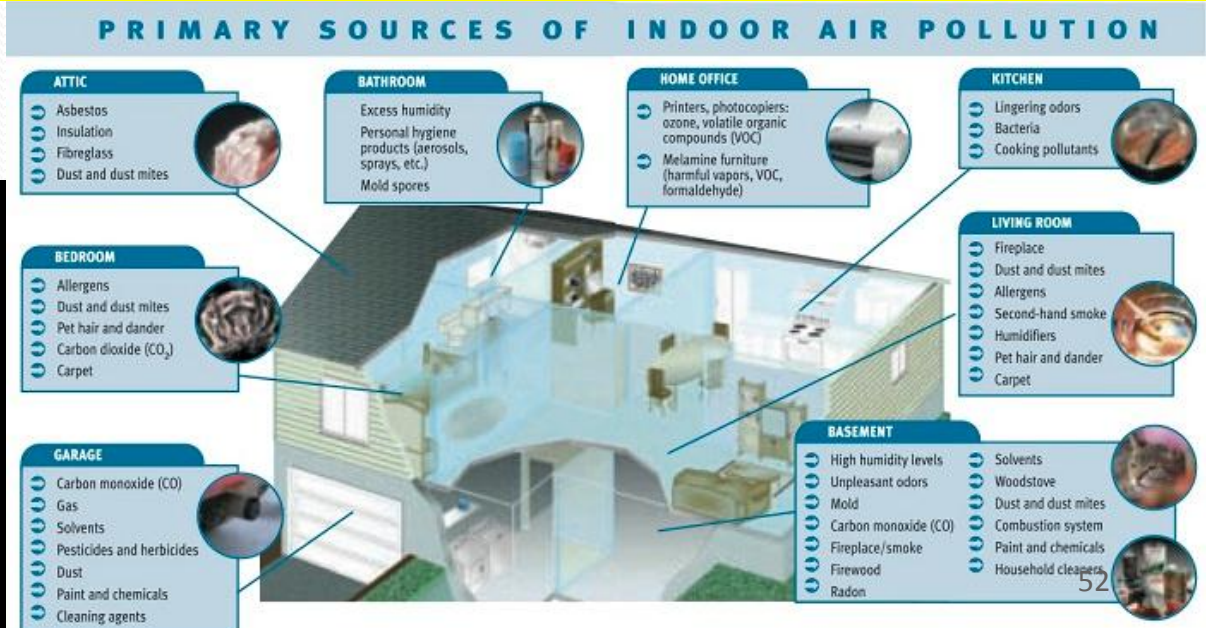
Different drugs with pros & cons

Different therapeutic agents

Common strategy & drugs

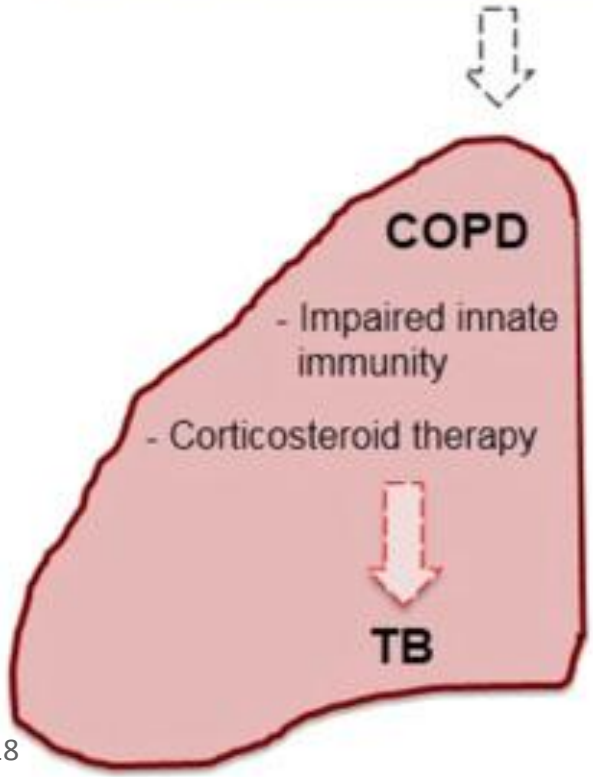


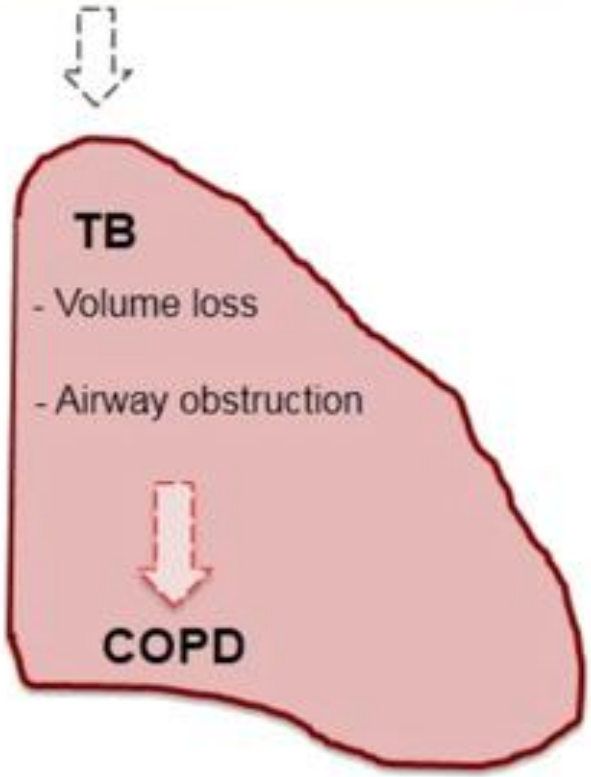
Smoking cessation and judicious use of current therapies will decrease the impact of COPD



Shared risk factors for TB and COPD

- Smoking
- Exposure to biomass fuel smoke
- Diabetes
- Nutritional status (vitamin D deficiency)





Treatment for COPD

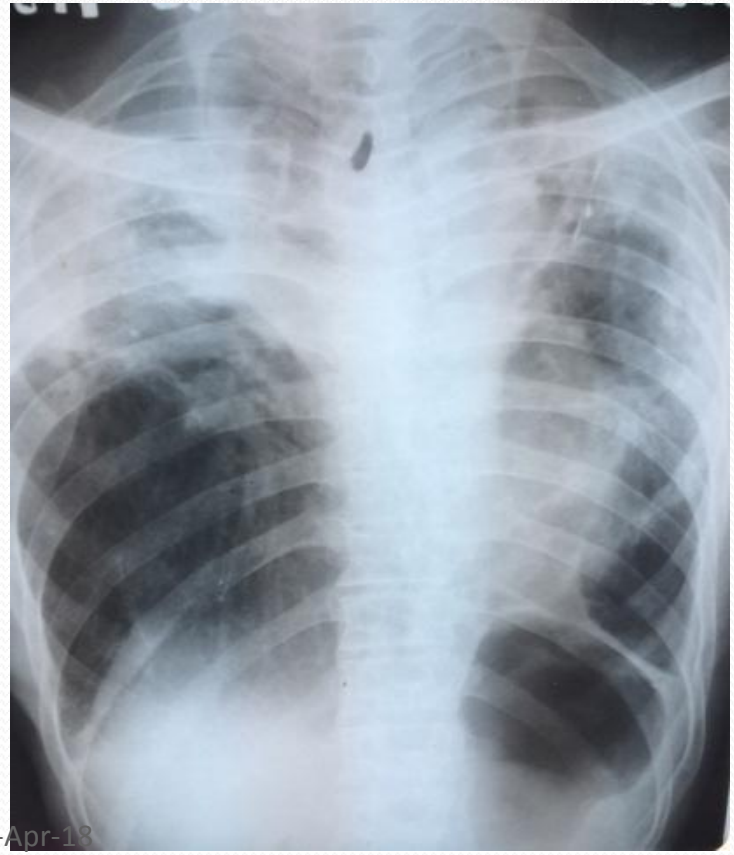
Not curable;

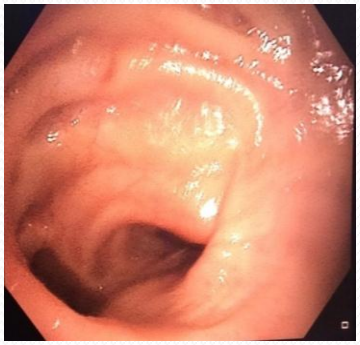
- To date, only smoking cessation and LTOT shown to influence mortality with LVRS in a selected subgroup

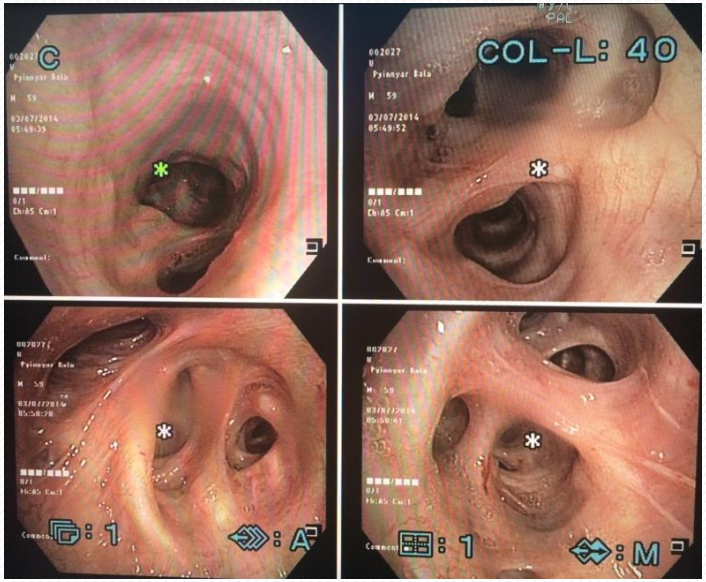
Treatment for TB

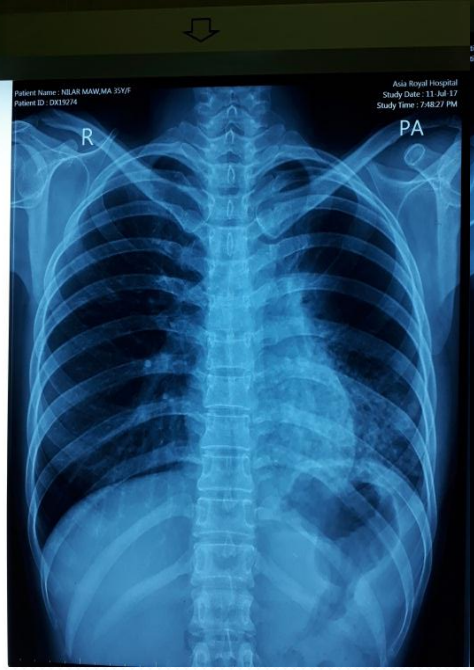
- Curable in the majority of TB cases with anti-TB Rx
- But, it is only the microbiological cure for TB.
- Occurrence of post TB pulmonary function impairment with consequent chronic airway diseases is much greater than previously believed

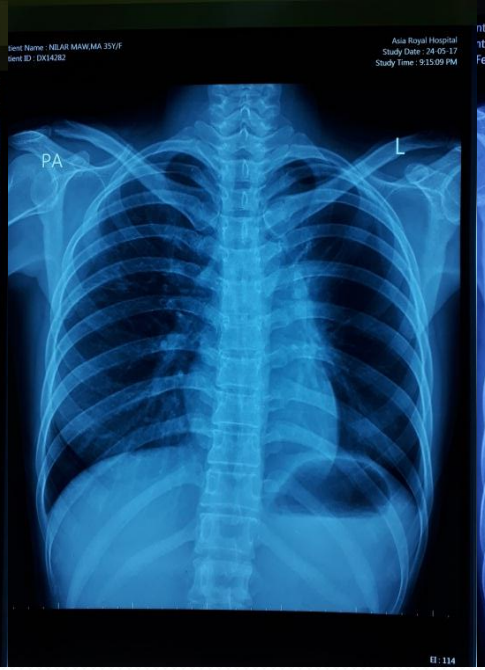
a patient with obstructive abnormality after successful TB treatment

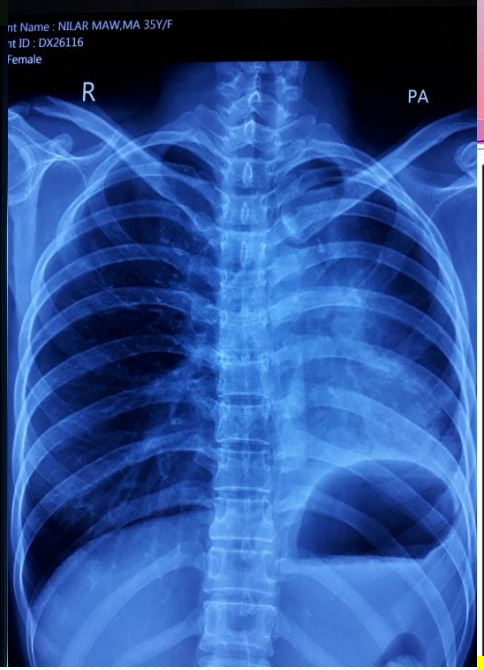




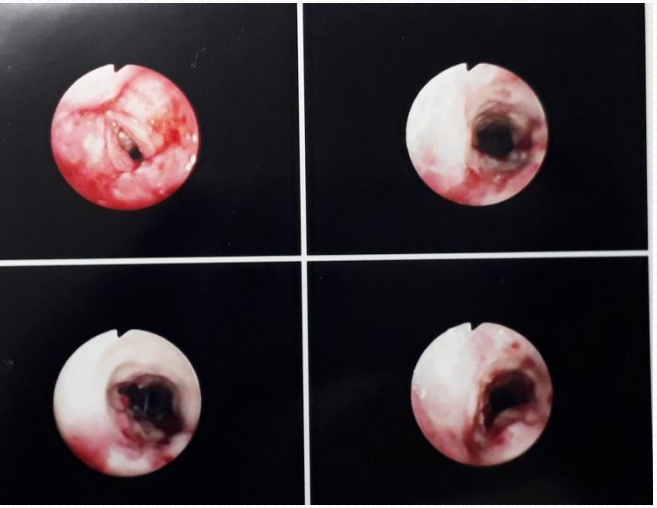


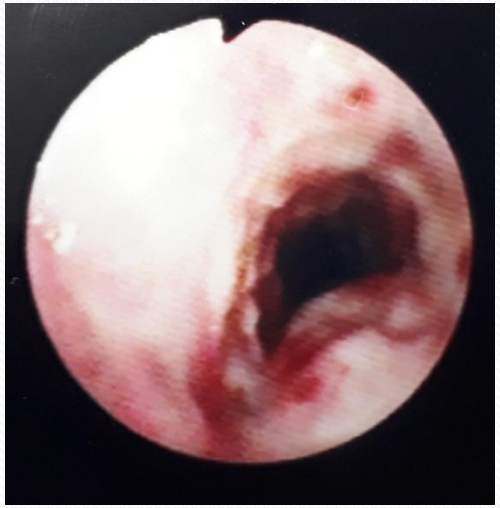


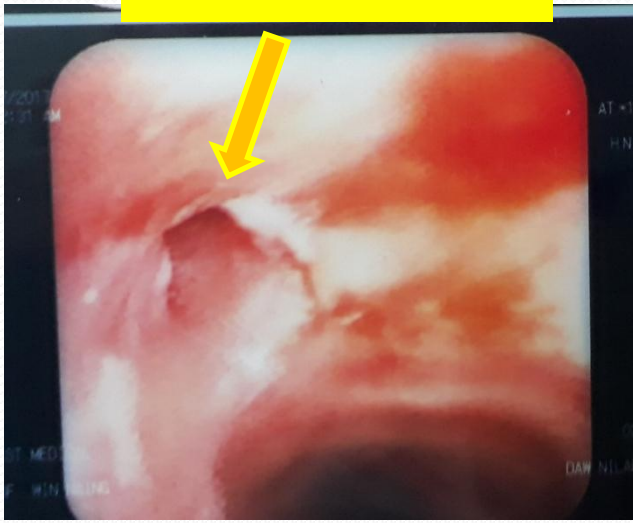




Left Main Bronchus

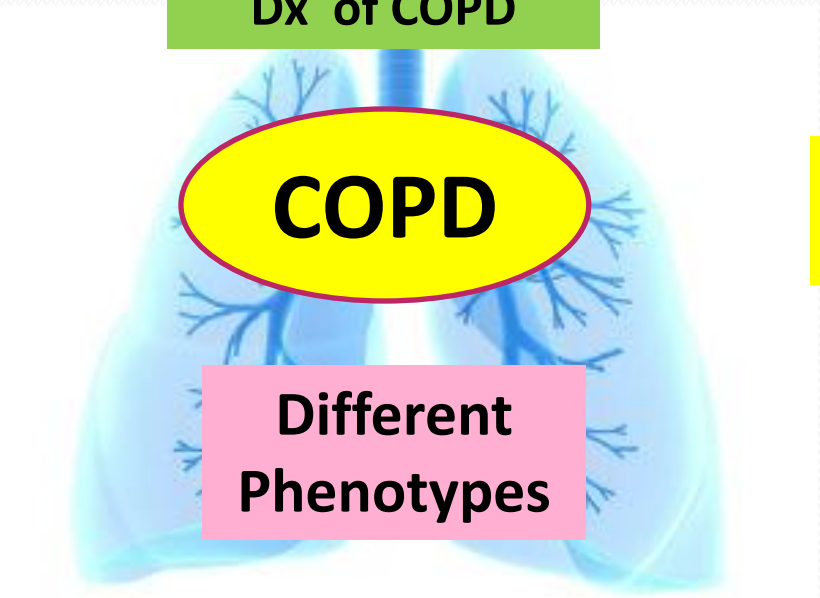






Assessment of COPD

Dx of COPD



Different causes

Extrapulmonary systemic effects

Diversity of counter measures

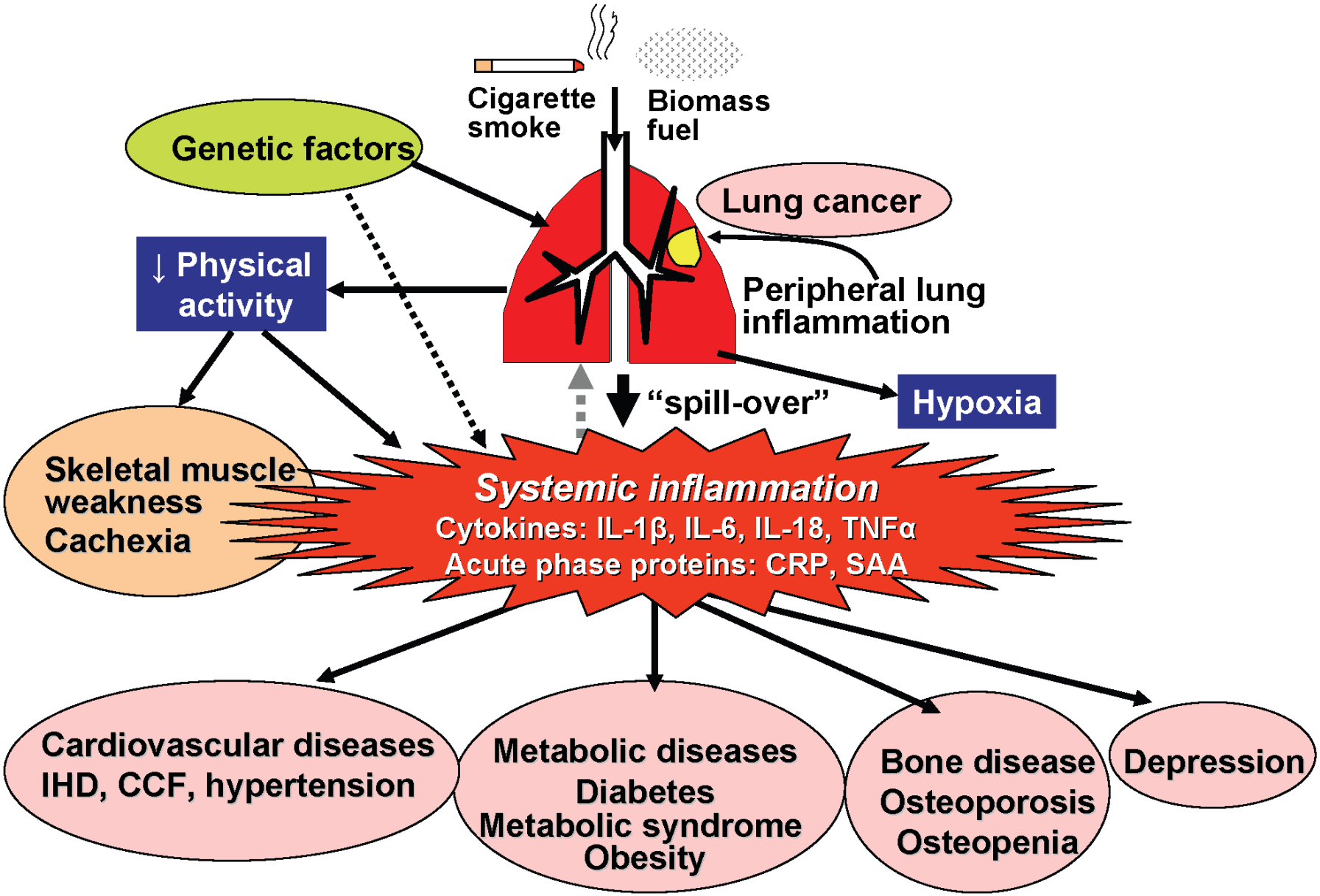
Different Phenotypes

Different drugs with pros & cons

Different therapeutic agents

Common strategy & drugs

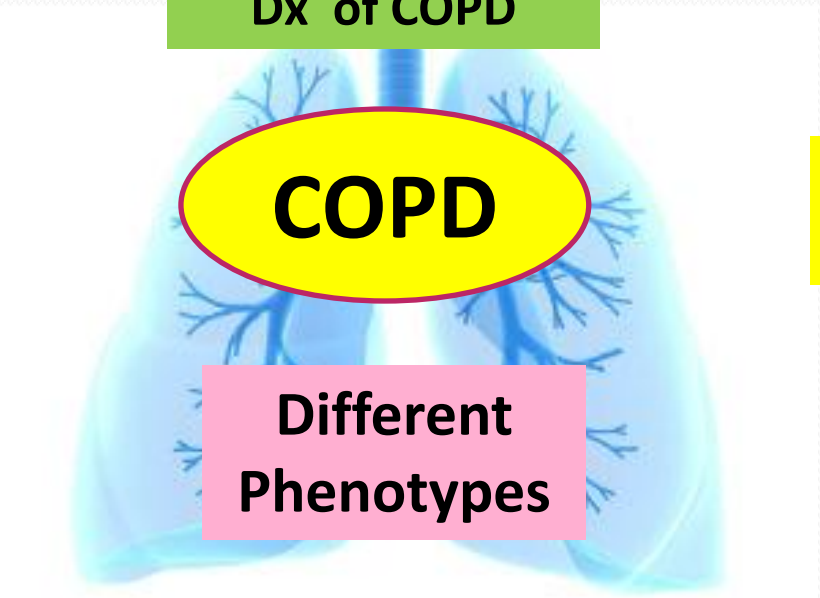
Genetics


Cigarette smoke
Biomass fuel
Genetic factors
Lung cancer
↓ Physical activity
Peripheral lung inflammation
"spill-over"
Hypoxia
Skeletal muscle weakness
Cachexia
Systemic inflammation
Cytokines: IL-1β, IL-6, IL-18, TNFα
Acute phase proteins: CRP, SAA
Cardiovascular diseases
IHD, CCF, hypertension
Metabolic diseases
Diabetes
Metabolic syndrome
Obesity
Bone disease
Osteoporosis
Osteopenia
Depression

- Not all smokers develop airflow obstruction or CA lung
- Genetic and host factors play an important role in the development of COPD
- But a significant portion of COPD goes beyond
- Complex interaction between genetic and environmental factors…may be
- So epigenetics and the mRNA complex need to be researched
- The “omics” revolution will help

Assessment of COPD

Dx of COPD



Different causes

Extrapulmonary systemic effects

Diversity of counter measures

Different Phenotypes

Different drugs with pros & cons

Different therapeutic agents

Common strategy & drugs

Genetics

Environments




Genome

Environment

Transcriptome

Proteome

Metabolome

Inflammation

Thrombosis
Hemorrhage

Fibrosis

Immune
response

Cell
proliferation

Apoptosis
Necrosis

Abnormal lung function

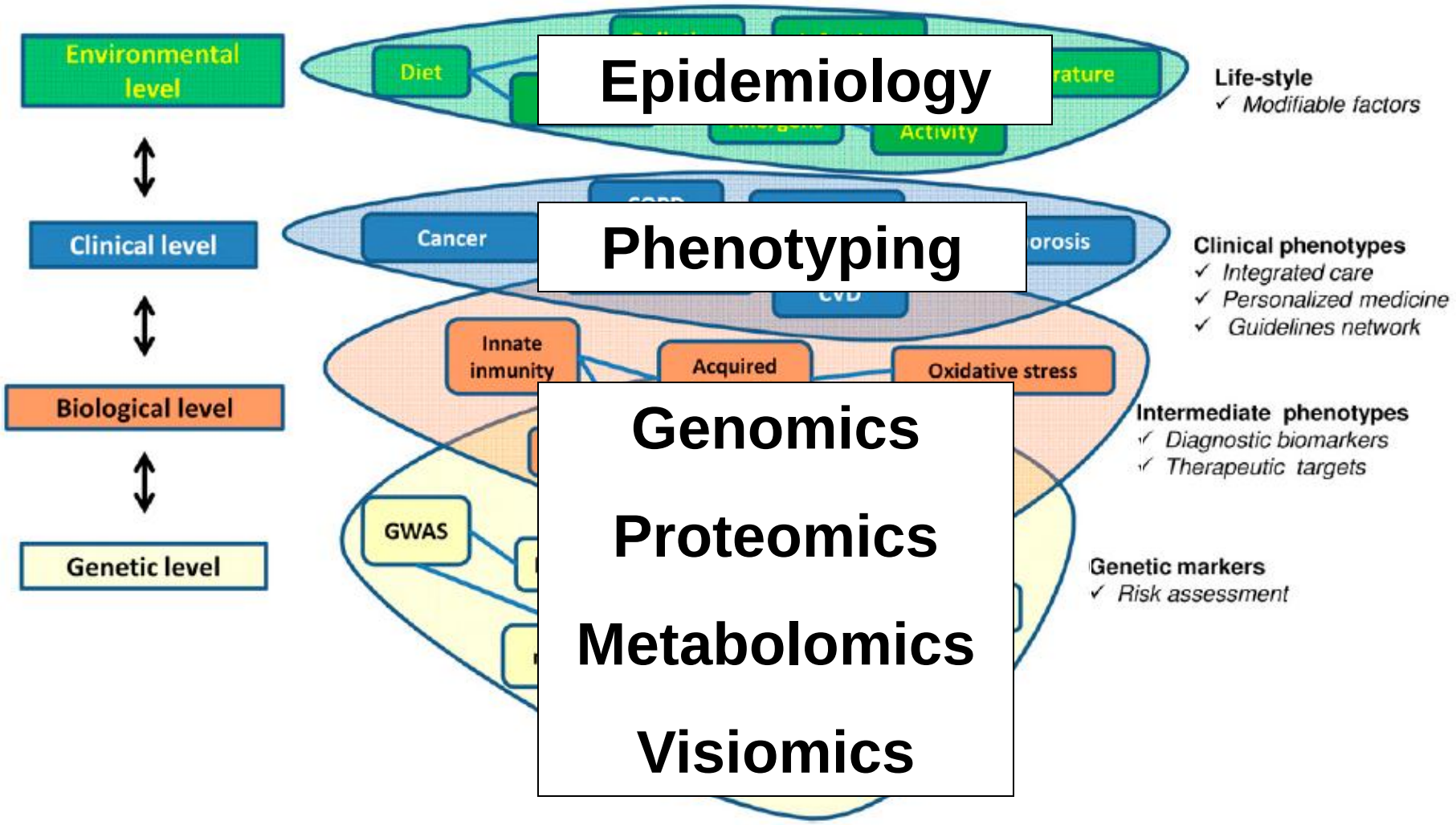
COPD

Modified from Loscalzo et al Mol Sys Bio 20007;3:124

- Current practice strongly relies on the prognosis, Dx & Rx of d/s using methods determined & averaged for the specific diseased cohort/population.
- Although this approach complies positively with most pts, misdiagnosis, Rx failure, relapse, and adverse drug effects are common occurrences
- These incidences can be explained by individual variation in the genome, transcriptome, proteome, & metabolome of a pt.
- Various "omics" approaches have investigated the influence of these factors on a molecular level, with the intention of developing personalized approaches to d/s Dx & Rx.

- Metabolomics, the newest “omics” & the closest to the observed phenotype, reflects changes occurring at all molecular levels, as well as influences resulting from other internal & external factors.
- Metabolomics can be applied to identify biomarkers related to the perturbation being investigated.
- Biomarkers can be used to develop personalized prognostic, diagnostic, and treatment approaches & can also be applied to the monitoring of d/s progression, Rx efficacy, predisposition to drug side effects & potential relapse.

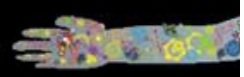
COPD complexity



Agusti A and Vestbo AJRCCM 20122;184:507

Take home message

- COPD is a heterogeneous disease
- COPD-pts display different phenotypes as a result of a complex interaction b/t various genetic & environmental factors.
- The degree of complexity requires analyses based on large datasets (eg. genomic assays) and novel computational biology approaches
- Some co-morbidities of COPD share pathobiological responses to injurious agents
- Comprehensive evaluation of pts for commonly occurring d/s is essential
- **Merging of specialties? Back to Holistic Medicine?**




mind
Health
body
spirit


RK

THANK YOU