2023.02.18 대한결핵 및 호흡기학회

제19차 천식연구회 · COPD연구회 공동 심포지엄

Key Changes of GOLD 2023 Report and Lancet Commission

문 지 용

한양대학교구리병원

Contents

An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations

The Rome Proposal

Bartolome R. Celli[1*], Leonardo M. Fabbri[2*‡], Shawn D. Aaron[3], Alvar Agusti[4,5,6,7], Robert Brook[8], Gerard J. Criner[9‡], Frits M. E. Franssen[10,11], Marc Humbert[12,13], John R. Hurst[14], Denis O'Donnell[15], Leonardo Pantoni[16], Alberto Papi[17,18], Roberto Rodriguez-Roisin[4,5], Sanjay Sethi[19], Antoni Torres[4,5,6,20], Claus F. Vogelmeier[21], and Jadwiga A. Wedzicha[22‡]

- **Definition** of "exacerbations of COPD" (ECOPD) in **GOLD 2021**

"An acute worsening of respiratory symptoms that results in additional therapy"

- **Severity** of ECOPD in **GOLD 2021**
  - **Mild**: inhaled short-acting bronchodilators
  - **Moderate**: antibiotics, systemic corticosteroids, or both
  - **Severe**: emergency room or hospitalization

Celli BR et al. Am J Respir Crit Care Med 2021;204:1251-8. [PMID: 34570991]

Table E1. Shortcomings in the current definition of exacerbation in patients with COPD and how they have been addressed in this revision.

	Current definition (1–4)	**Addressed in the updated Rome definition**

Celli BR et al. Am J Respir Crit Care Med 2021;204:1251-8. [PMID: 34570991]

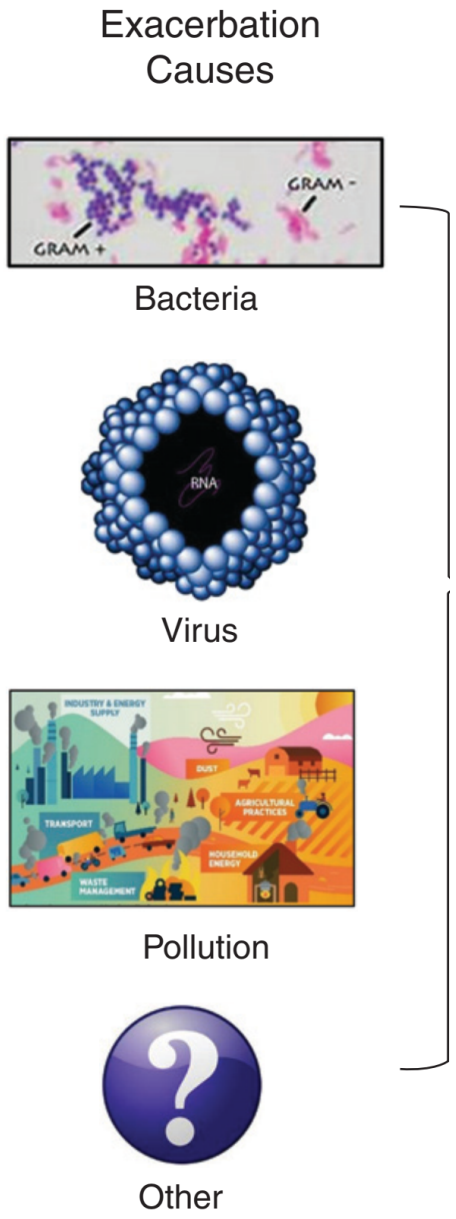


Figure 1. Causes, pathobiological mechanisms, and pathophysiological consequences in an exacerbation of chronic obstructive pulmonary disease (7, 35). CRP = C-reactive protein.

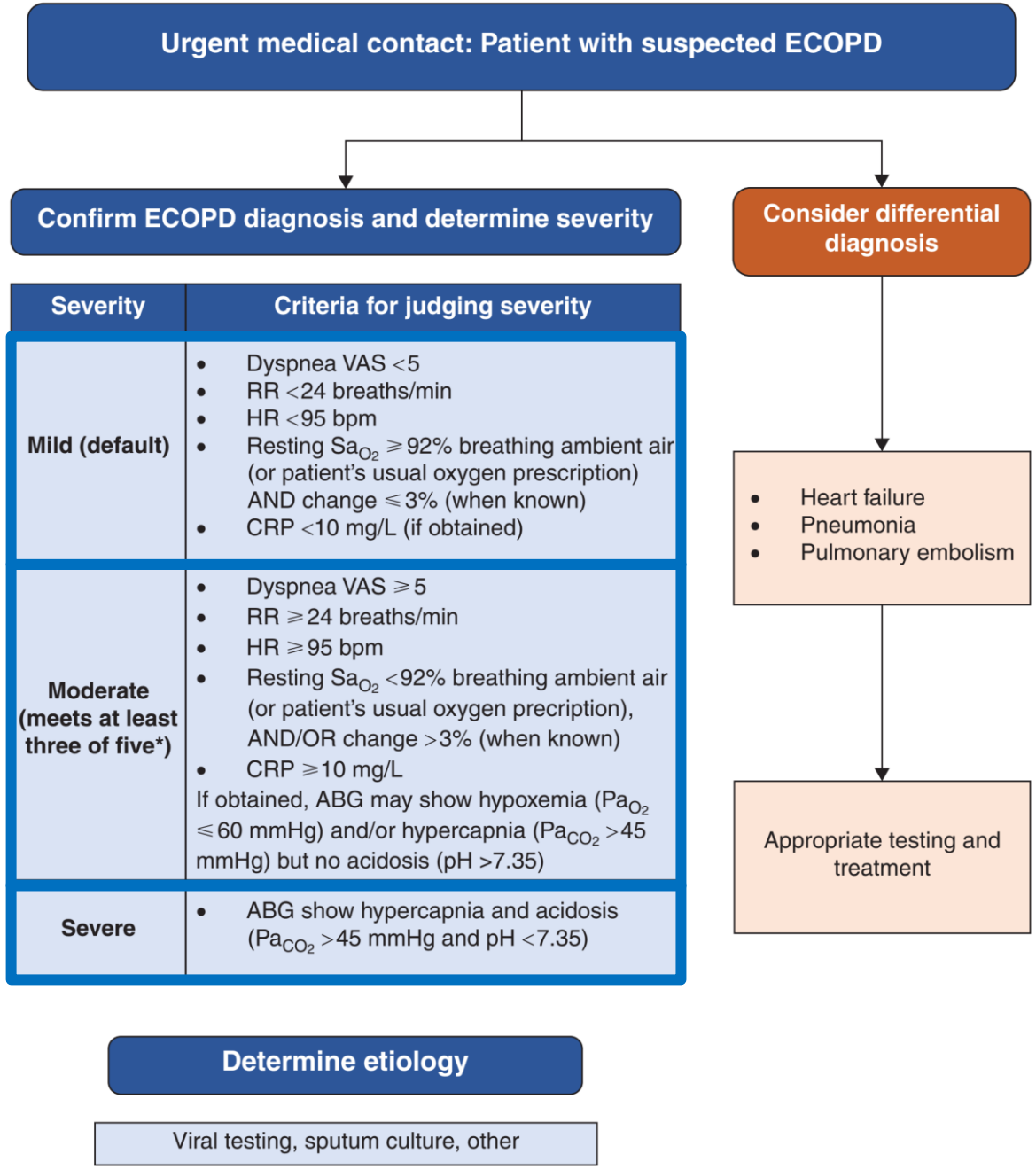
Celli BR et al. Am J Respir Crit Care Med 2021;204:1251-8. [PMID: 34570991]

Table 1. The Rome Proposal for an Updated Definition and Severity Classification of COPD Exacerbations

Definition	
Diagnostic approach	

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; VAS = visual analog scale.

Celli BR et al. Am J Respir Crit Care Med 2021;204:1251-8. [PMID: 34570991]



Celli BR et al. Am J Respir Crit Care Med 2021;204:1251-8. [PMID: 34570991]

Table E5 Panel of questions addressing the potential acute illnesses to be considered in the differential diagnosis of COPD exacerbations. Green color identifies the items that reached consensual agreement. Yellow color identifies the items with consensual disagreement on the statement. White background identifies items with no consensus.

	Condition	Median	IQR
45	Abscess hypopharynx	1	2
46	Acute vocal cord paralysis	1	3
47	Acute bronchorrhea in bronchiectasis	4	4
48	Acute asthma attack	6	3
49	Tracheobronchomalacia	3	4
50	Intraluminal tumors	3	3
51	Lung abscess	2	1
52	Foreign body/mucous plugs	2	3
53	Acute interstitial pneumonitis	3	4
54	Lobar pneumonia	7	3
55	Pleural effusion	5	3
56	Exacerbation of pulmonary fibrosis	4	3
57	Pneumothorax	6	5
58	Pulmonary embolism	7	4
59	Anemia	4	4
60	Arrhythmia	5.5	3
61	Constrictive pericarditis	2	3
62	Pericardial effusion	2	4
63	Myocardial infarction	6	3
64	Heart failure	8	2
65	Metabolic acidosis	3	4
66	Valvular rupture in the heart	2	2
67	Acute Guillain-Barré syndrome	1	1
68	Diaphragmatic paralysis	2	2
69	Thyroid storm	0	2
70	Anxiety/panic attack	6	3
71	Somatiform disorder	3	4
72	Delirium	3	4

Celli BR et al. Am J Respir Crit Care Med 2021;204:1251-8. [PMID: 34570991]

Table E6. Panel of questions to define the threshold values useful to separate mild from moderate severity exacerbations.

	Threshold value questions	Median	IQR
73	The maximum period for worsening of symptoms to be considered a COPD exacerbation is 14 days	7	4
74	A dyspnea threshold value of <5 cm in a VAS that ranges from 0 (no dyspnea) to 10 cm (most dyspnea ever felt) can help differentiate a lesser from a more severe degree of severity of a COPD exacerbation	8	2
75	A respiratory rate threshold value of <24 breaths per min can help differentiate a lesser from a more severe degree of severity of a COPD exacerbation	8	1
76	A heart rate threshold value of <95 bpm can help differentiate a lesser from a more severe degree of severity of a COPD exacerbation	7	2
77	An oxygen saturation threshold value of SaO_2 >92% breathing ambient air AND a change in SaO_2 <3% (when known) can help differentiate a lesser from a more severe degree of severity of a COPD exacerbation	8	1
78	A CRP threshold value of <10 mg/L can help differentiate a lesser from a more severe degree of severity of a COPD exacerbation.	7	2

	Integration of the variables	
79	When applied in clinical research to define the severity of an exacerbation, rank the following three statements in order of preference, where 1 = most preferred, and 3 = least preferred.	
A	A numerical integration of **all five** variables is needed to define the severity of an exacerbation.	First choice 5 Second choice 5 Third choice 8
B	A numerical integration of **four of the five** variables is needed to define the severity of an exacerbation.	First choice 2 Second choice 10 Third choice 3
C	A numerical integration of **three of the five** variables is needed to define the severity of an exacerbation.	First choice 8 Second choice 2 Third choice 5

Celli BR et al. Am J Respir Crit Care Med 2021;204:1251-8. [PMID: 34570991]

Rome Criteria for Exacerbation of Chronic Obstructive Pulmonary Disease: Not Built in a Day

To the Editor:

- The proposed definition **discounts cough** as an important symptom
- It is not uncommon for individuals with **severe COPD** to have significant **dyspnea at baseline**.
- The inclusion of self-reported **physical exam findings** may also be problematic.
  - Not all patients can accurately and reliably count their **heart rate** and **respiratory rate**, especially if this is not measured over a certain minimum time period.
  - Do these physical exam findings need to be abnormal **for a certain period of time**?

Bhatt SP. Am J Respir Crit Care Med 2022;205:1124-5. [PMID: 35196475]

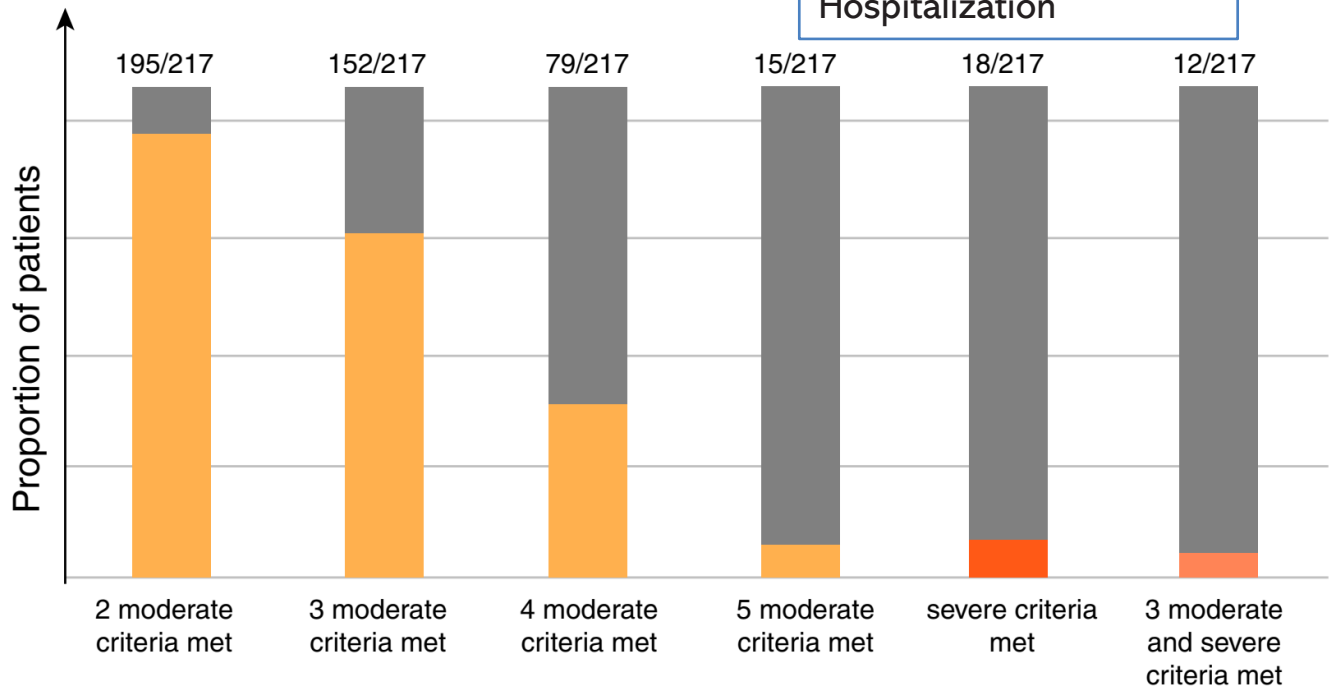
Rome severity criteria applied to BACE cohort

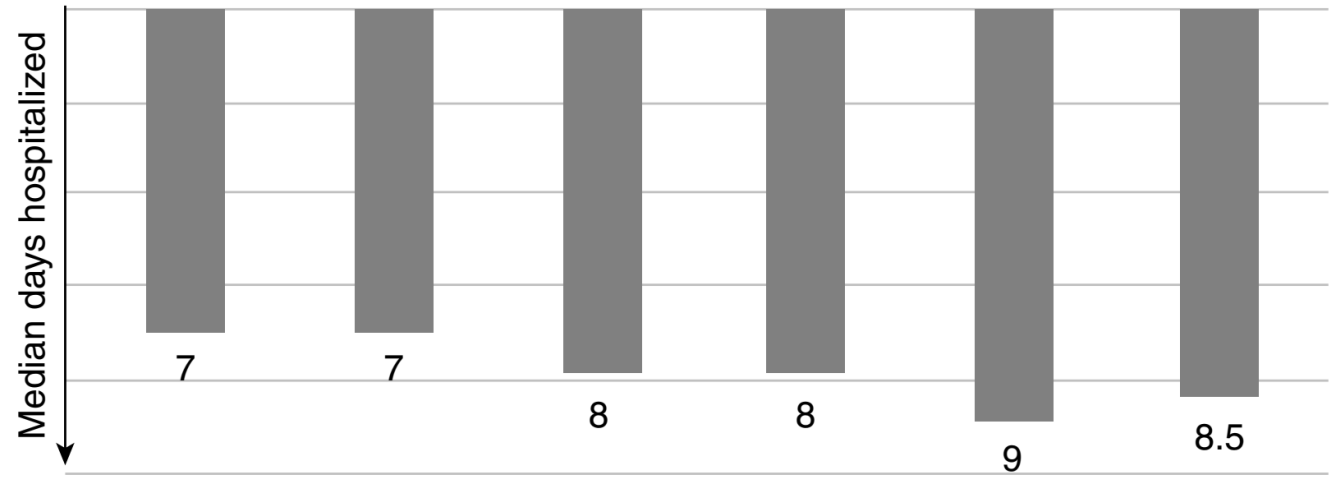
Azithromycin for Acute Exacerbations Requiring Hospitalization

Chronic Obstructive Pulmonary Disease Exacerbations: Do All Roads Lead to Rome?

To the Editor:

Rome Criteria	n/N
HR ⩾ 95/min	111/217
RR ⩾ 24/min	88/217
CRP ⩾ 10mg/ml	130/217
P/F < 310	122/217
Pa_{CO_2} > 45	65/217
pH < 7.35	19/217





Ramakrishnan S et al. Am J Respir Crit Care Med 2022;205:1125-6. [PMID: 35196480]

The CICERO (Collaboration In COPD ExaceRbatiOns) Clinical Research Collaboration

Wim Janssens [1] and Mona Bafadhel[2], Chairs of the CICERO Clinical Research Collaboration[3]

TABLE 1 CICERO (Collaboration In COPD ExaceRbatiOns) objectives

Objective 1	Establish European CICERO centres to take part in longitudinal data collection cohort CATALINA study
Objective 2	European CICERO expert consultation survey of what/when to measure during and after hospitalised COPD exacerbation event
Objective 3	Establish standardisation of data collection, processing and storage of all samples
Objective 4	Set up CICERO resources for members, partners, patients and the public
Objective 5	Create change in clinical practice *via* European Respiratory Society approved task forces
Objective 6	CICERO extension with further funding for interventional studies

Janssens W et al. Eur Respir J 2020;55 [PMID 32139591]

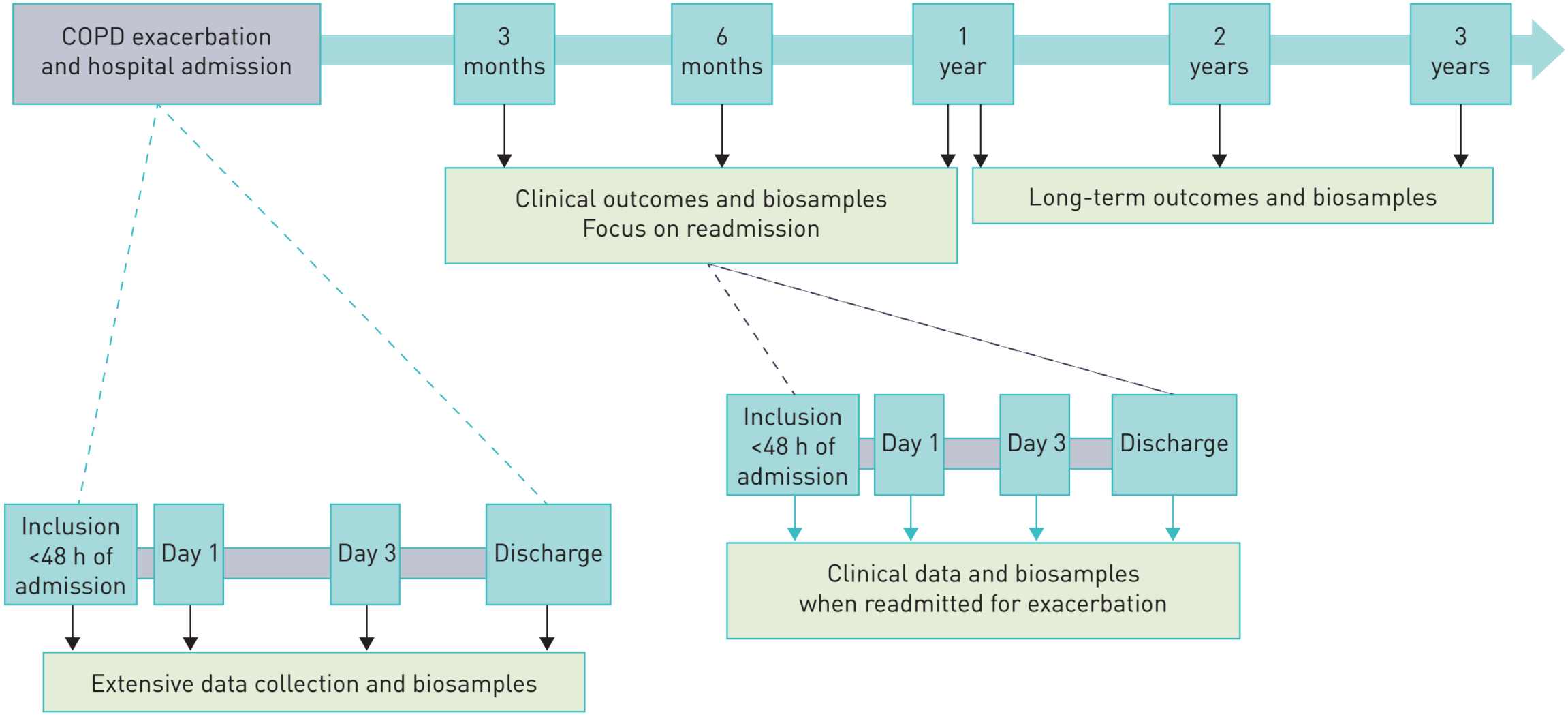


FIGURE 1 Proposed study design o CATALINA.

- a prospective observational cohort study designed to recruit 2000 patients hospitalised with acute COPD exacerbations with longitudinal follow-up.

Janssens W et al. Eur Respir J 2020;55 [PMID 32139591]

Archivos de Bronconeumología 58 (2022) T159–T170

Sociedad Española de Neumología y Cirugía Torácica SEPAR

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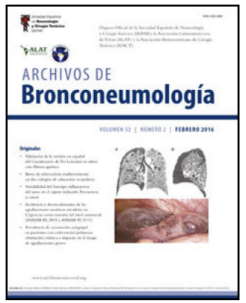


SEPAR's voice

[Translated article] Spanish COPD Guidelines (GesEPOC) 2021 Update. Diagnosis and Treatment of COPD Exacerbation Syndrome

Juan José Soler-Cataluña[a,b,*], Pascual Piñera[c], Juan Antonio Trigueros[d], Myriam Calle[e], Ciro Casanova[f], Borja G. Cosío[b,g], Josè Luis López-Campos[b,h], Jesús Molina[i], Pere Almagro[j], José-Tomás Gómez[k], Juan Antonio Riesco[b,l], Pere Simonet[m], David Rigau[n], Joan B. Soriano[b,o], Julio Ancochea[b,o], Marc Miravitlles[b,p], representing the GesEPOC 2021 working group[1]

- **COPD exacerbation syndrome** (**CES**) is defined as **an episode of clinical instability** that occurs in a patient with COPD as a result of **worsening of expiratory airflow limitation or the underlying inflammatory process**, and is characterized by an **acute worsening** of the individual's respiratory symptoms **relative to baseline**.

Soler-Cataluna JJ et al. Arch Bronconeumol 2022;58:159-70. [PMID: 34172340]

- **Treatment failure**: when **worsening** of symptoms occurs during the **CES itself** and **requires additional treatment**. Average recovery time after CES is approximately 2 weeks. However, some patients do not fully recover until 4-6 weeks.
- **Relapse**: when **further worsening** of symptoms occurs between the end of CES treatment and **the next 4 weeks**.
- **Recurrence**: when symptoms reappear within 1 year of the preceding CES, after a period of relative good health. **At least 4 weeks** must have passed **after completing the previous CES** treatment or **6 weeks after onset of symptoms**. Recurrences are considered **new episodes of CES**.

Key points.

COPD exacerbation is considered a syndrome resulting from different etiopathogenic mechanisms, all of which have a similar clinical expression.
In circumstances where it is difficult to discriminate whether clinical worsening is a result of COPD or a comorbidity, both processes should be diagnosed and treated.
Pneumonia is included within CES.
The severity of the CES should be assessed according to the baseline risk stratification (low or high risk) and the severity of the acute episode (level of dyspnea, level of consciousness, respiratory rate and gas exchange).
The treatment of choice for CES is short-acting and rapid-acting bronchodilators.
Systemic corticosteroids are suggested for moderate CES and recommended for all patients with severe or very severe CES. Their efficacy is greater when the peripheral blood eosinophil count is > 300 cells/mm^3
Other treatment should be guided by severity level and the identification of different treatable traits.

CES: chronic obstructive pulmonary disease exacerbation syndrome; COPD: chronic obstructive pulmonary disease.

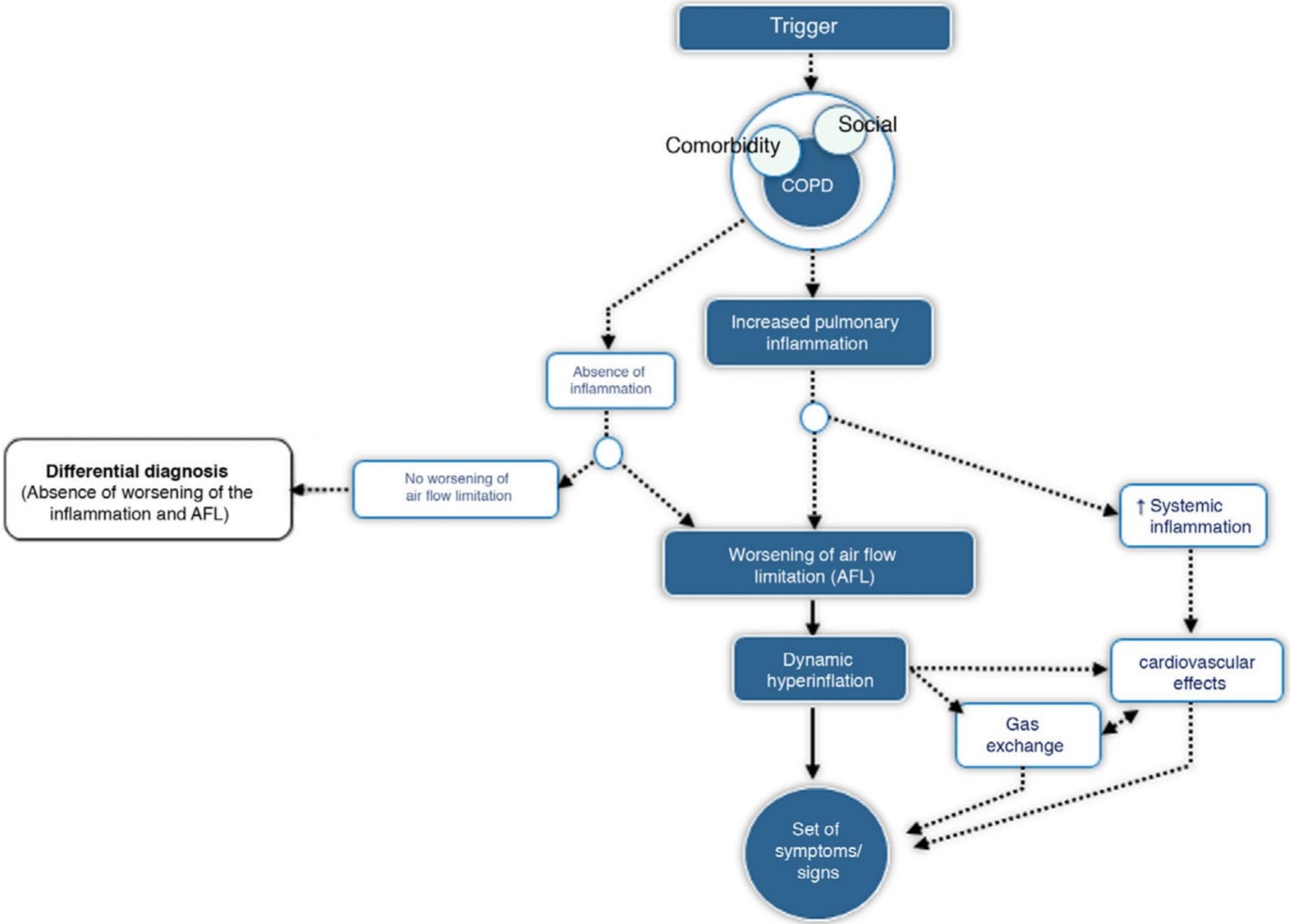


Fig. 1. Pathophysiology of COPD exacerbation syndrome.

COPD: chronic obstructive pulmonary disease.

Soler-Cataluna JJ et al. Arch Bronconeumol 2022;58:159-70. [PMID: 34172340]

Table 2
Differential diagnosis.

Respiratory causes:
- Pulmonary embolism
- Pneumothorax
- Pleural effusion
- Chest trauma
Cardiac causes:
- Heart failure
- Cardiac arrhythmias
- Acute ischemic heart disease
Other:
- Anxiety
- Upper airway obstruction

Soler-Cataluna JJ et al. Arch Bronconeumol 2022;58:159-70. [PMID: 34172340]

Risk stratification in COPD patients (GesEPOC 2021)

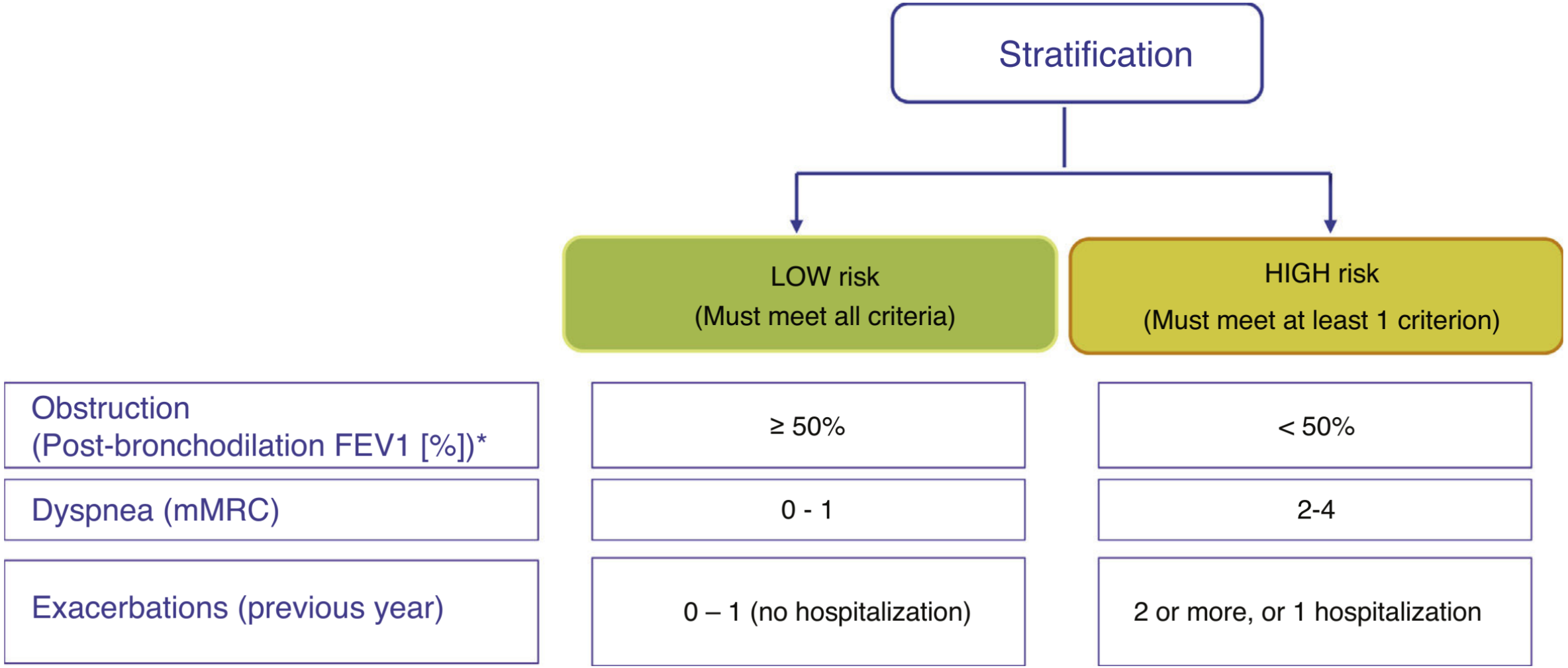
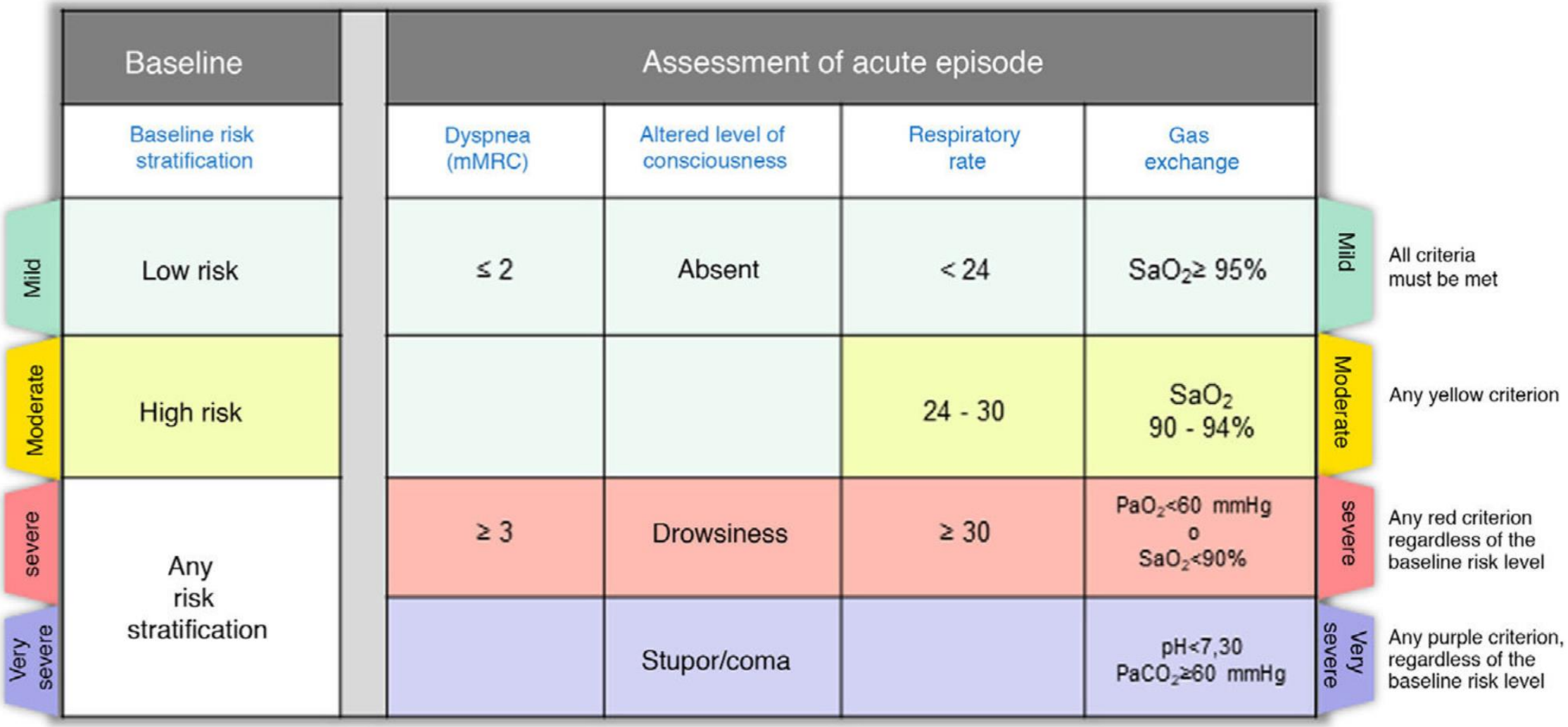


Fig. 1. Risk stratification in COPD patients.

Miravitlles M et al. Arch Bronconeumol 2022;58:69-81 [PMID 33840553]

COPD exacerbation syndrome (CES) severity criteria



Baseline		Assessment of acute episode					
	Baseline risk stratification	Dyspnea (mMRC)	Altered level of consciousness	Respiratory rate	Gas exchange		
Mild	Low risk	≤ 2	Absent	< 24	SaO_2 ≥ 95%	Mild	All criteria must be met
Moderate	High risk			24 - 30	SaO_2 90 - 94%	Moderate	Any yellow criterion
severe	Any risk stratification	≥ 3	Drowsiness	≥ 30	PaO_2<60 mmHg o SaO_2<90%	severe	Any red criterion regardless of the baseline risk level
Very severe			Stupor/coma		pH<7,30 $PaCO_2$≥60 mmHg	Very severe	Any purple criterion, regardless of the baseline risk level

Soler-Cataluna JJ et al. Arch Bronconeumol 2022;58:159-70. [PMID: 34172340]

PULMONARY PERSPECTIVE

Definition and Nomenclature of Chronic Obstructive Pulmonary Disease
Time for Its Revision

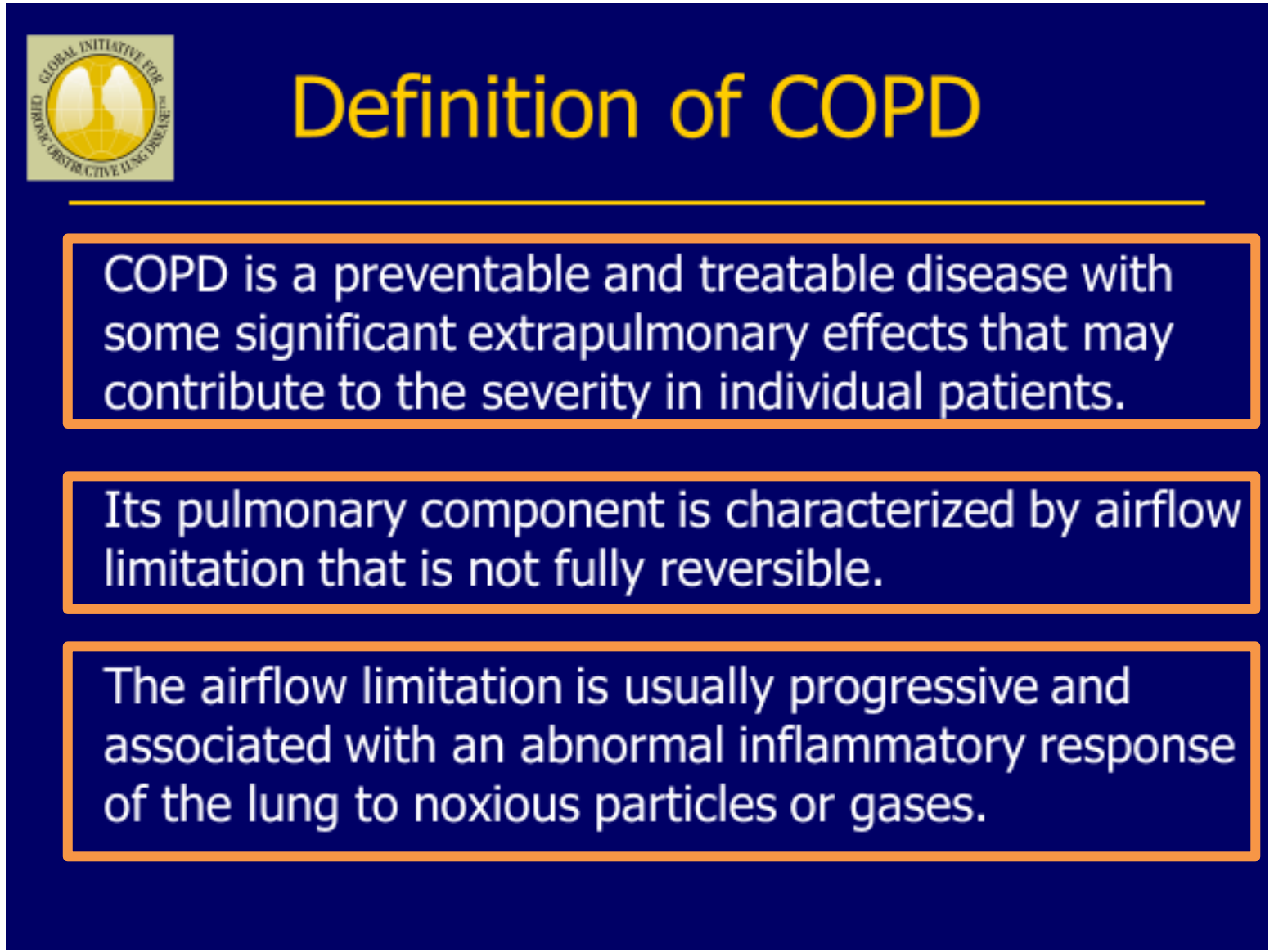
Bartolome Celli[1], Leonardo Fabbri[2], Gerard Criner[3], Fernando J. Martinez[4], David Mannino[5], Claus Vogelmeier[6], Maria Montes de Oca[7], Alberto Papi[2], Don D. Sin[8], MeiLan K. Han[9], and Alvar Agusti[10]

[1]Pulmonary Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [2]Department of Translational Medicine, University of Ferrara, Ferrara, Italy; [3]Department of Thoracic Medicine and Surgery, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania; [4]Joan and Sanford I. Weill Department of Medicine, Weill Cornell Medicine, New York, New York; [5]Division of Pulmonary, Critical Care, and Sleep Medicine, University of Kentucky College of Medicine, Lexington, Kentucky; [6]Pulmonary and Critical Care Medicine, Department of Medicine, University Medical Center University of Marburg, German Center for Lung Research (DZL), Philipps University Marburg, Marburg, Germany; [7]Hospital Universitario de Caracas, Universidad Central de Venezuela and Centro Médico de Caracas, Caracas, Venezuela; [8]Division of Respiratory Medicine, Centre for Heart Lung Innovation, St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada; [9]University of Michigan Health System, Ann Arbor, Michigan; and [10]Cátedra Salud Respiratoria, Universitat de Barcelona; Respiratory Institute, Hospital Clinic, Barcelona; IDIBAPS, CIBERES, Barcelona, Spain

Celli B et al. Am J Respir Crit Care Med 2022;206:1317-25 [PMID 35914087]

Previous Definitions of COPD

- 2007 - 2010



GOLD 2007

Previous Definitions of COPD

- **2011 - 2016**

Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is 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**. Exacerbations and comorbidities contribute to the overall severity in individual patients

- **2017 - 2019**

Chronic Obstructive Pulmonary Disease (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 Report 2011-2019

Definition of COPD (GOLD 2022) & Its limitation

- COPD definition by GOLD (in 2020 – 2022): "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** and influenced by host factors including abnormal **lung development**. Significant comorbidities may have an impact on morbidity and mortality"

- An important limitation, however, may be that the current COPD definition and taxonomy **fail to identify the disorder at its early stages**, before airflow limitation becomes evident.

- It also defines **the entity as a single disease**, **limiting the role of different causes** of COPD leading to the same functional or physiologic abnormality.

Celli B et al. Am J Respir Crit Care Med 2022;206:1317-25 [PMID 35914087]

Causes of COPD

- **Genetic** COPD (**COPD-G**)
- COPD Due to Abnormal Lung **Development** (**COPD-D**)
- Environmental COPD
  - **Cigarette** smoking COPD (**COPD-C**)
  - Biomass and **pollution** exposure COPD (**COPD-P**)
- COPD Due to **Infections** (**COPD-I**)
- COPD and **Asthma** (**COPD-A**)
- COPD of **Unknown** Cause (**COPD-U**)
- COPD of **Mixed** Causes (**COPD-M**)

Celli B et al. Am J Respir Crit Care Med 2022;206:1317-25 [PMID 35914087]

Proposed Definition of COPD

- To agree on a new acronym would be to start again on a road that has taken us a long time and effort to pursue. **Keeping the term COPD** but **adjusting its meaning** to include the expanding knowledge of the disease should make specific goals and better management of patients more achievable.

- Current definition of diabetes
  - "**Diabetes** is **a group** of metabolic diseases **characterized by** hyperglycemia **resulting from** defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with **long-term damage, dysfunction, and failure of** different organs, especially the eyes, kidneys, nerves, heart, and blood vessels"

- COPD should be defined as follows:
  - **COPD** is a **heterogeneous** **lung condition** characterized by **chronic respiratory symptoms** (dyspnea, cough, expectoration) due to **persistent abnormalities of the airways** (bronchitis, bronchiolitis), and/or **alveoli** (emphysema), that often results in **progressive airflow limitation**.

Celli B et al. Am J Respir Crit Care Med 2022;206:1317-25 [PMID 35914087]

Contents

The Lancet Commissions

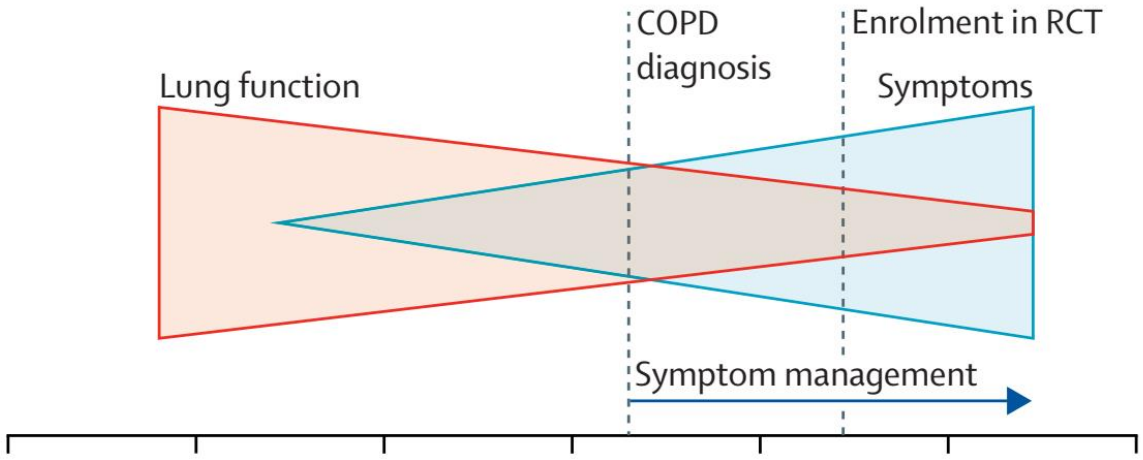
Towards the elimination of chronic obstructive pulmonary disease: a *Lancet* Commission

Daiana Stolz, Takudzwa Mkorombindo, Desiree M Schumann, Alvar Agusti, Samuel Y Ash, Mona Bafadhel, Chunxue Bai, James D Chalmers, Gerard J Criner, Shyamali C Dharmage, Frits M E Franssen, Urs Frey, MeiLan Han, Nadia N Hansel, Nathaniel M Hawkins, Ravi Kalhan, Melanie Konigshoff, Fanny W Ko, Trisha M Parekh, Pippa Powell, Maureen Rutten-van Mölken, Jodie Simpson, Don D Sin, Yuanlin Song, Bela Suki, Thierry Troosters, George R Washko, Tobias Welte, Mark T Dransfield

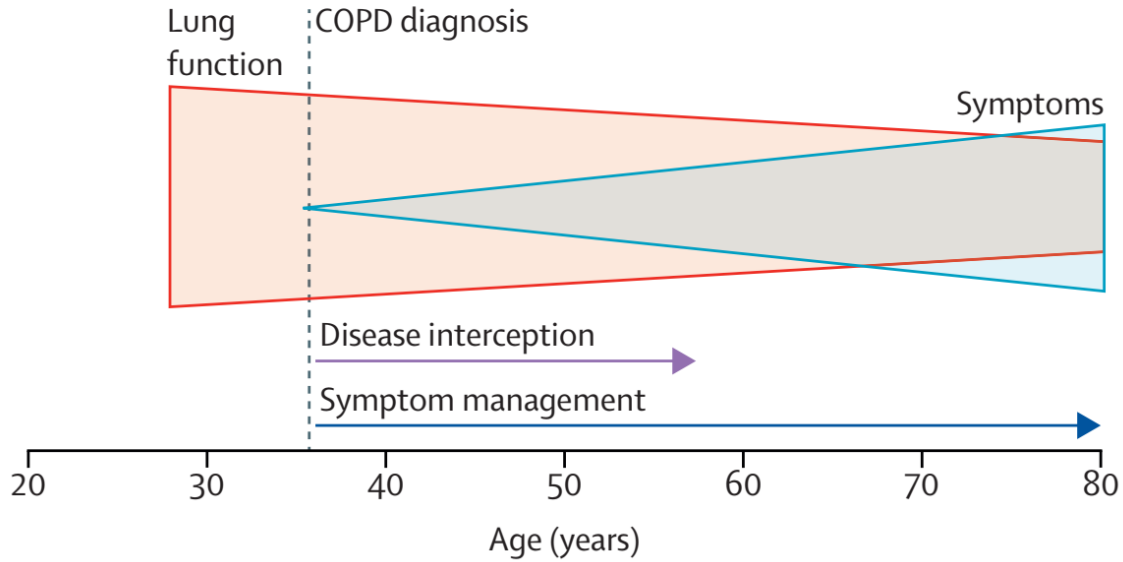
Stolz D et al. Lancet 2022;400:921-72. [PMID: 36075255]

The importance of early diagnosis to eliminate COPD

Current



Future



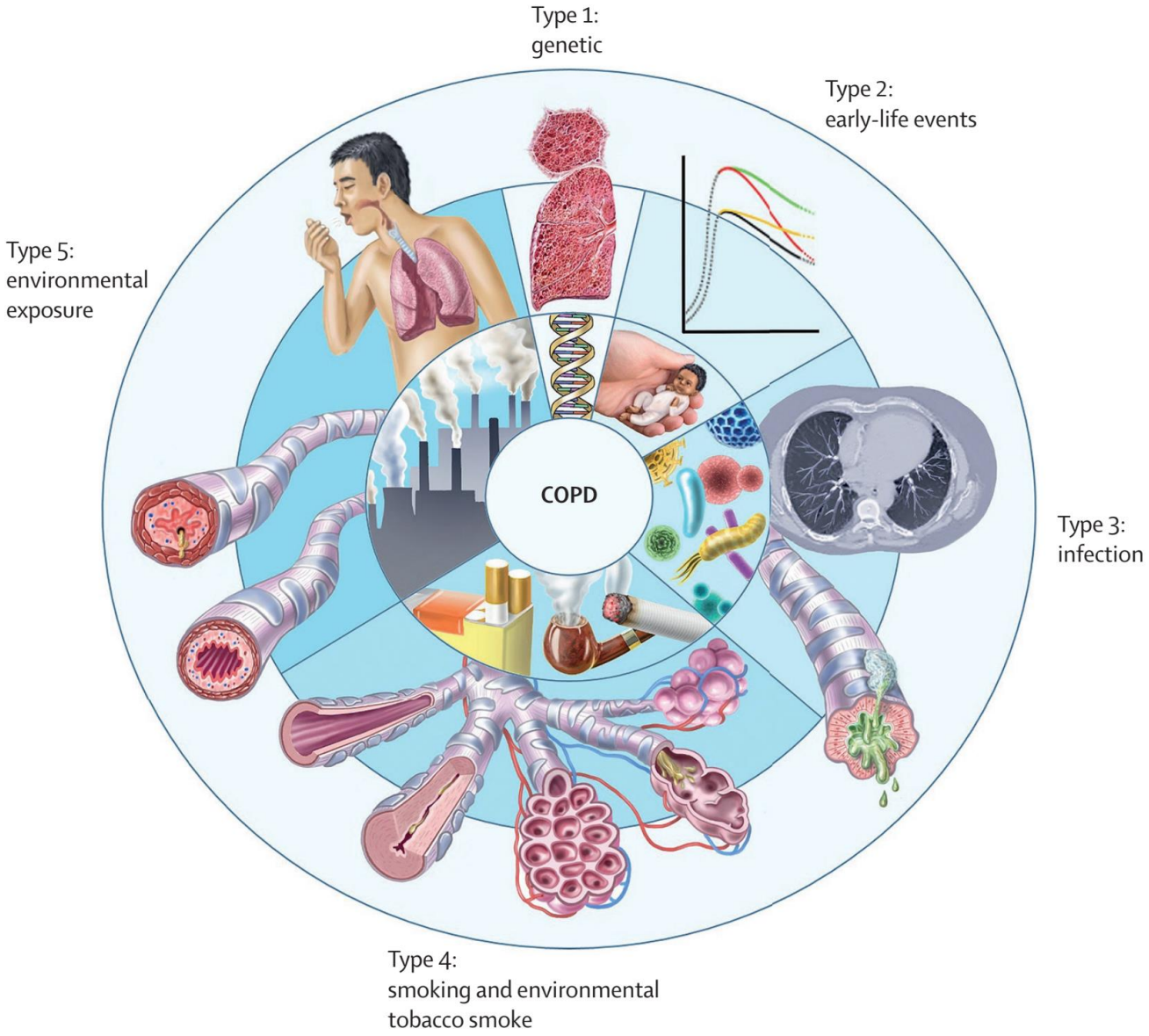
Stolz D et al. Lancet 2022;400:921-72 [PMID 36075255]

Example of Pulmonary Hypertension

- One example in respiratory medicine is pulmonary hypertension, which was the focus of **WHO** meetings in **1960 on cor pulmonale** and in **1973 on primary pulmonary hypertension**.
- The clinical classification of pulmonary hypertension has been developed and refined since these pioneer proposals.
- Conditions associated with pulmonary hypertension are **grouped** on the basis of **broadly similar pathomechanisms, clinical presentations, haemodynamic findings, and management**.
- In the past 50 years, this classification has evolved alongside scientific knowledge and provided a strong basis for **successful therapeutic innovations** in **group 1** (pulmonary arterial hypertension) and **group 4** (chronic thromboembolic pulmonary hypertension) disease.

Brusselle GG et al. Lancet 2022;400:869-71 [PMID 36075257]

Proposed classification of COPD according to major risk factors



***Panel:* Classification of COPD by the *Lancet* Commission on COPD**

Type 1: genetically determined COPD
1.1 α_1 antitrypsin deficiency
1.2 Telomerase reverse transcriptase mutations
1.3 Other genetic variants

Type 2: COPD related to early-life events
2.1 Prematurity (chronic lung disease of prematurity, bronchopulmonary dysplasia)
2.2 Childhood asthma

Type 3: infection-related COPD
3.1 Childhood respiratory infections
3.2 Tuberculosis-associated COPD
3.3 HIV-associated COPD

Type 4: COPD related to smoking or vaping
4.1 Tobacco smoking
4.2 In-utero exposure to tobacco smoke
4.3 Passive smoking (childhood and adult)
4.4 Vaping or e-cigarette smoking
4.5 Cannabis smoking

Type 5: environmental exposure-related COPD
5.1 Exposure to indoor air pollutants
5.2 Outdoor air pollution and smog
5.3 Wildfire smoke
5.4 Occupational exposures (to vapours, gases, dusts, or fumes)

COPD=chronic obstructive pulmonary disease.

COPD-G

COPD-D

COPD-A

COPD-I

COPD-C

COPD-P

COPD-U

COPD-M

Stolz D et al. Lancet 2022;400:921-72 [PMID 36075255]
Brusselle GG et al. Lancet 2022;400:869-71 [PMID 36075257]

Causal variants, causal genes, and functional evidence for key genetic associations with COPD

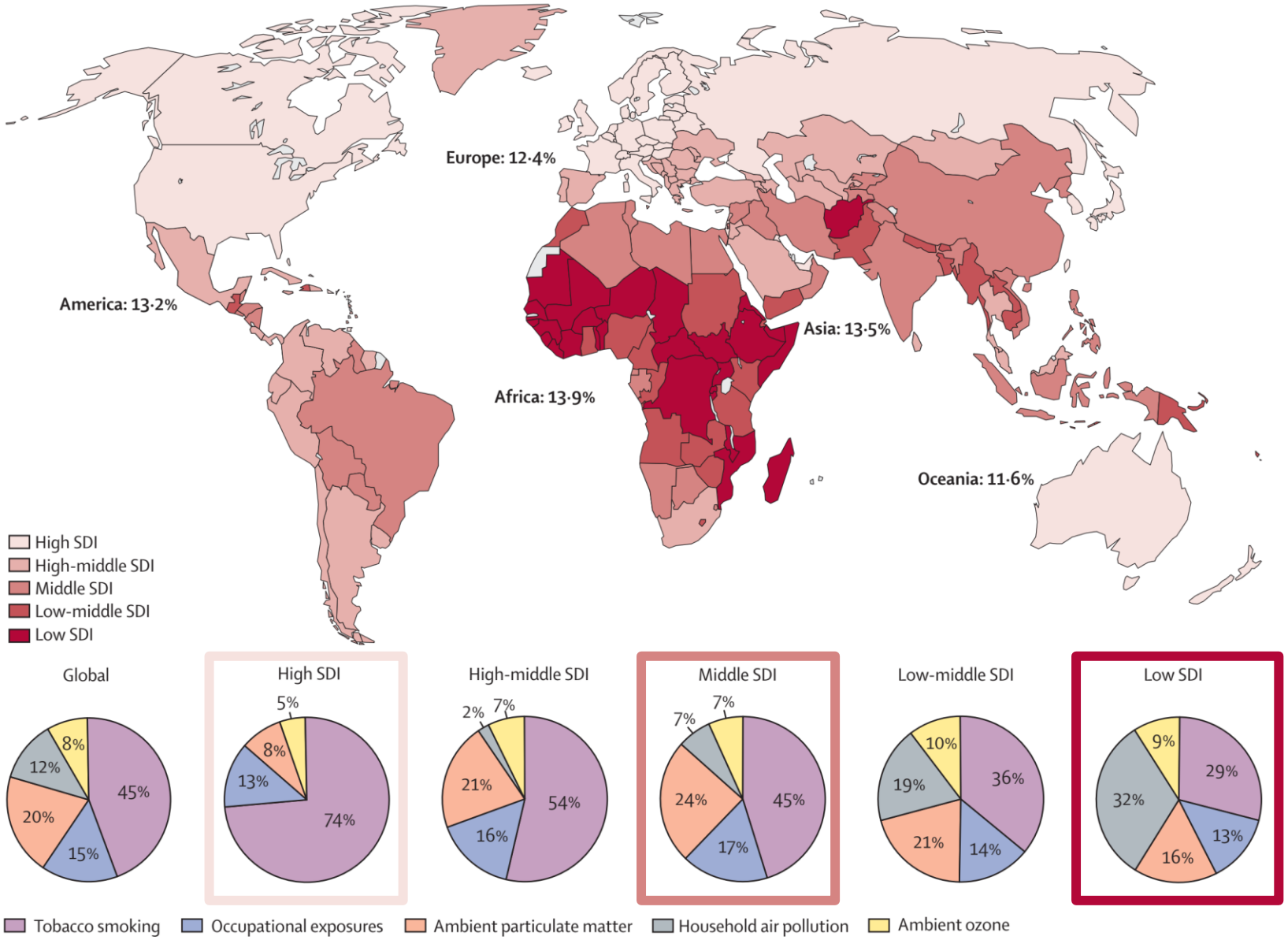
	Gene name	Evidence for causal variant(s) and gene	Functional evidence or implications
AGER	Advanced glycosylation end-product specific receptor	The protein-altering (non-synonymous) *AGER* coding variant rs2070600 is associated with sRAGE protein levels (ie, pQTL)	sRAGE, encoded by *AGER*, is associated with emphysema and lung function decline[69]
HHIP	Hedgehog-interacting protein	Functional variants (eg, rs6537296, rs1542725) are associated with *HHIP* expression levels (ie, QTL); regulatory interactions have been identified through chromosomal conformation capture[56]	The *Hhip* haploinsufficient mouse has increased susceptibility to cigarette smoke, age-related emphysema, and lymphocytic inflammation[56,57,70]
FAM13A	Family with sequence similarity 13 member A	*FAM13A* expression, functional variants,[71] and eQTL (eg, rs2013701) have been reported	*FAM13A* has effects on the Wnt–β-catenin pathway[64] and induces reactive oxygen species;[72] *Fam13a*-null (*Fam13a*$^{-/-}$) mice are more resistant to chronic cigarette smoke-induced and elastase-induced emphysema than are *Fam13a*$^{+/+}$ mice[64]
SFTPD	Surfactant protein D	The protein-altering (non-synonymous) *SFTPD* coding variant rs721917 is associated with SFTPD protein levels (ie, pQTL)	SFTPD has an immunomodulatory role and is a biomarker for COPD risk and progression[15,73–75]
TGFB2	Transforming growth factor beta 2	Variant rs1690789 is an eQTL for *TGFB2*; this functional variant has been identified in lung fibroblasts[76]	With associations at other loci, studies of COPD-related traits have implicated genes in the *TGFB2* superfamily[13,77]
SERPINA1	Serpin family A member 1	Variant rs28929474 in *SERPINA1* is a pQTL for α1-antitrypsin; homozygosity for rs28929474 is the most common cause of α1-antitrypsin deficiency[24]	Discovery of deficiency for the gene product of *SERPINA1* in 1963 led to the protease–antiprotease hypothesis in COPD and α1-antitrypsin augmentation therapy[22,24]
TERT	Telomerase reverse transcriptase	Rare *TERT* variants affecting telomere length (eg, rs372511089) have been identified; *TERT* mutations segregate in families with emphysema[78]	Telomere pathway mutations can predispose to COPD and pulmonary fibrosis alone or combined pulmonary fibrosis and emphysema[79]

COPD=chronic obstructive pulmonary disease. eQTL=expression quantitative trait locus. pQTL=protein quantitative trait locus. SNP=single-nucleotide polymorphism. sRAGE=soluble receptor for advanced glycation end products.

Table: **Causal variants, causal genes, and functional evidence for key genetic associations with COPD**

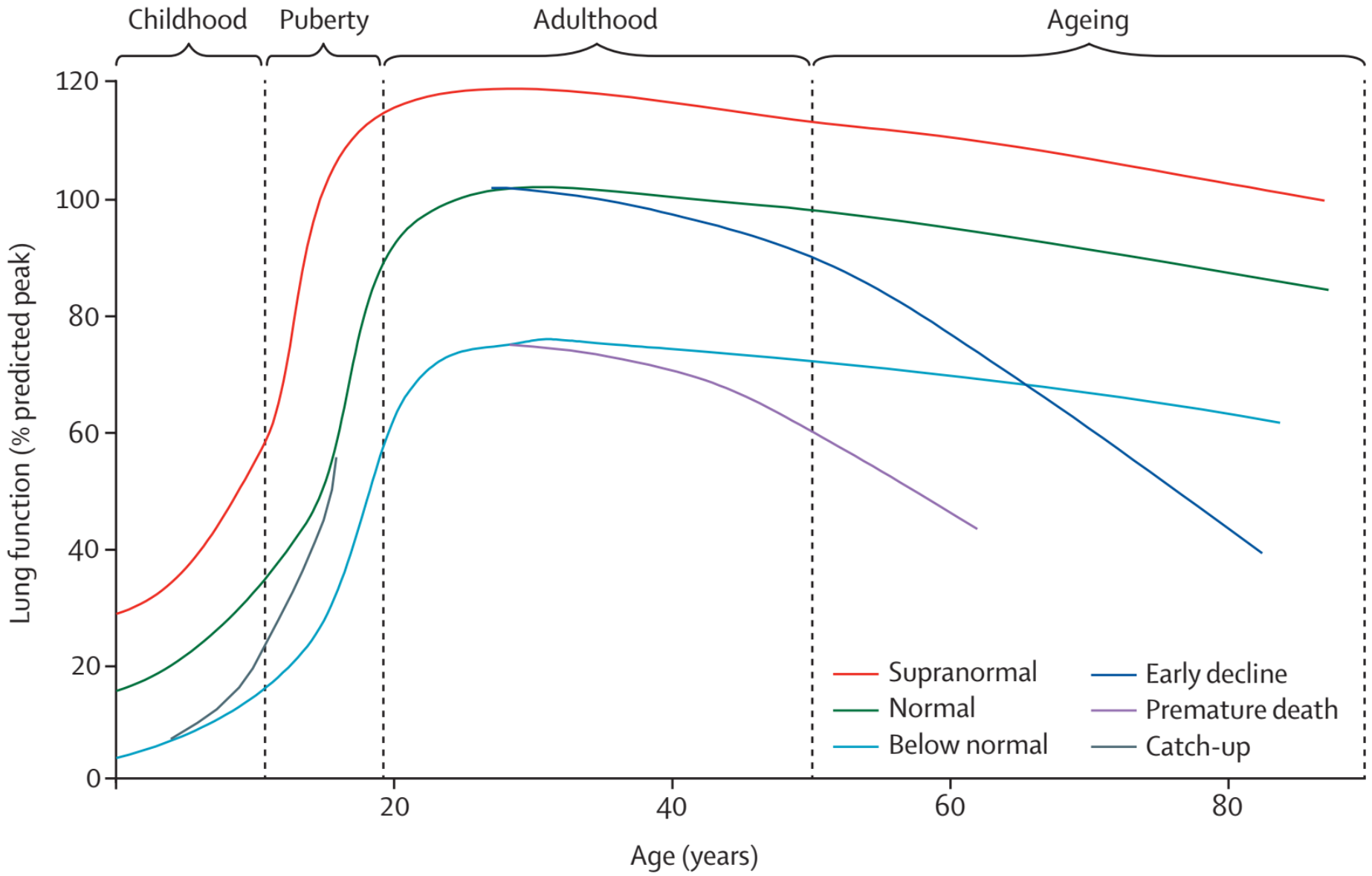
Cho MH. Genetics of chronic obstructive pulmonary disease: understanding the pathobiology and heterogeneity of a complex disorder. Lancet Respir Med 2022;10:485-96. [PMID 35427534]

Global risk factors associated with COPD according to sociodemographic index



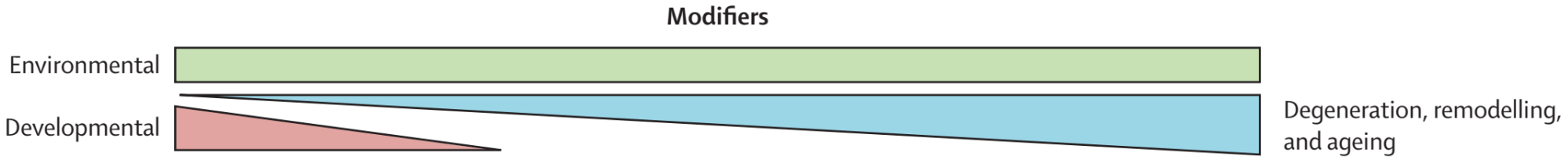
Yang IA. Chronic obstructive pulmonary disease in never-smokers: risk factors, pathogenesis, and implications for prevention and treatment. Lancet Respir Med 2022;10:497-511. [PMID 35427530]

Potential lung function trajectories



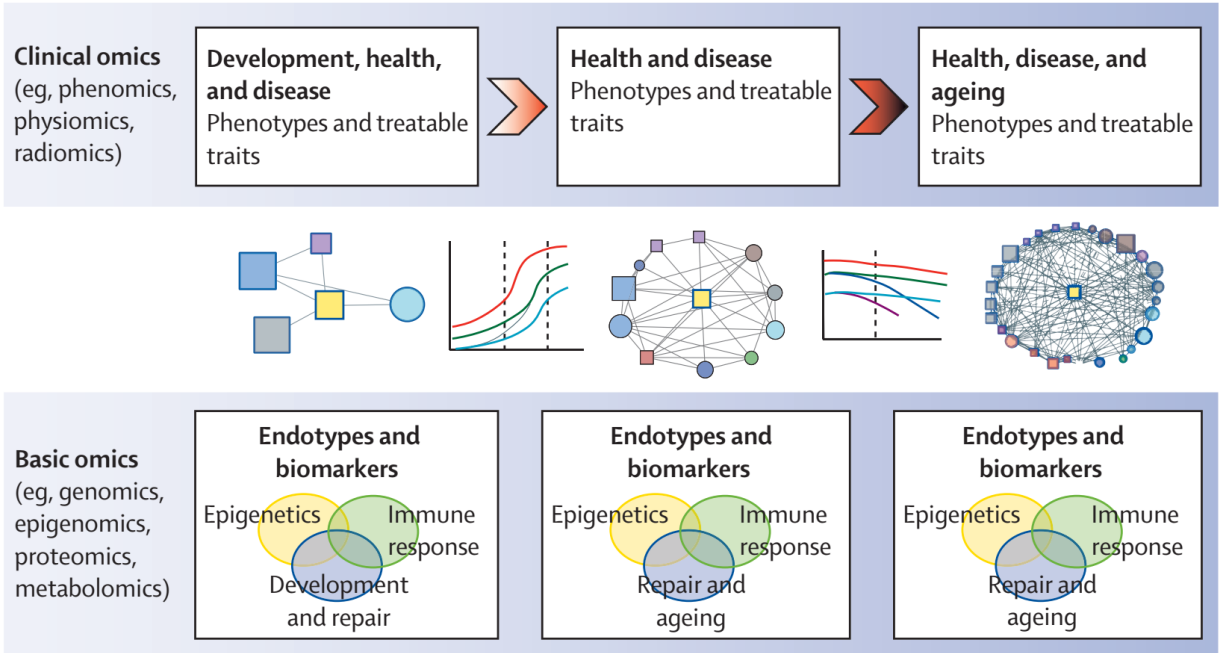
Agusti A et al. Lancet Respir Med 2022;10:512-24 [PMID 35427533]

Lung function trajectories across the life course



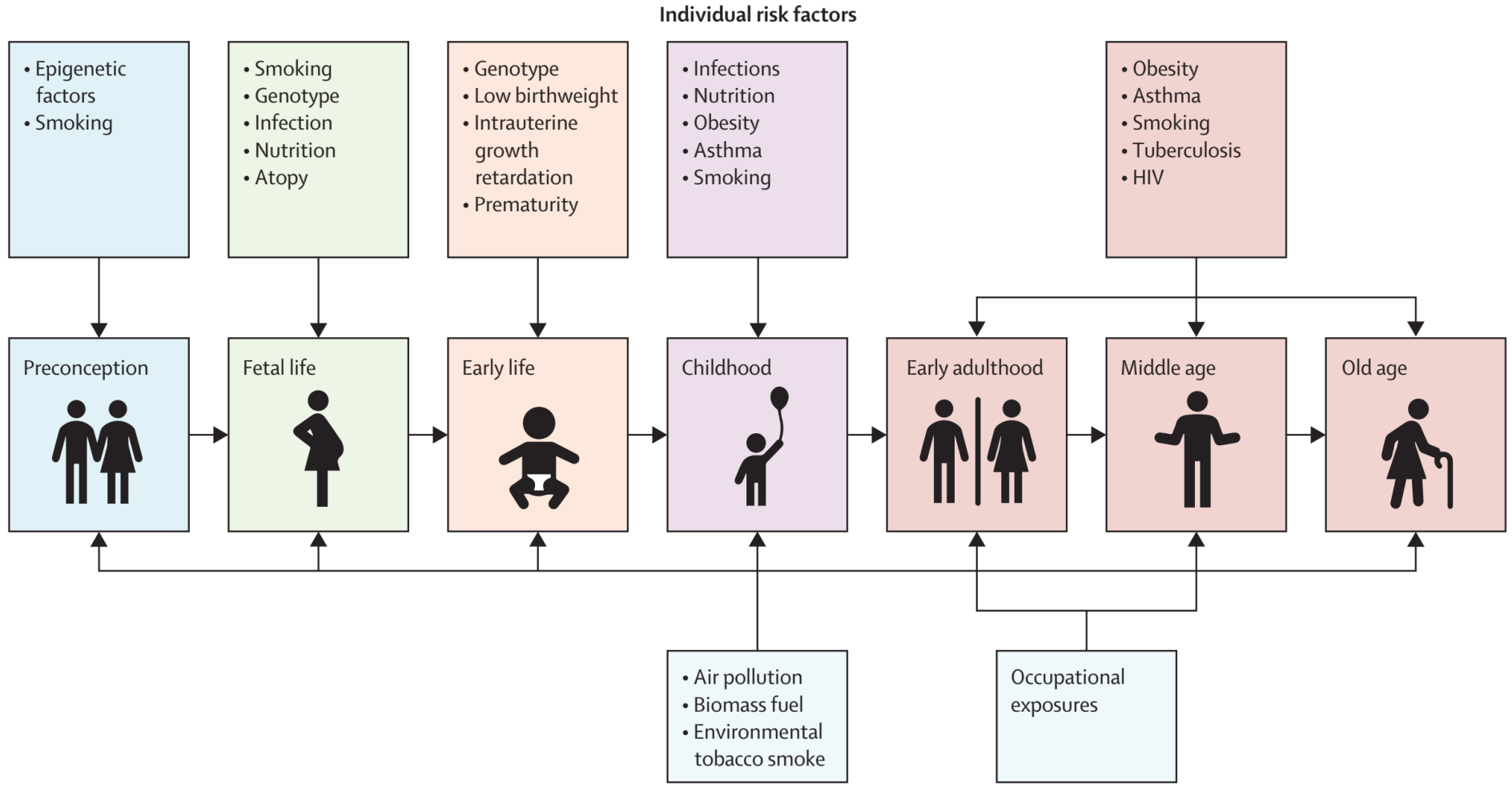
Stolz D et al. Lancet 2022;400:921-72 [PMID 36075255]

A GETomics approach to understanding COPD and other chronic human diseases



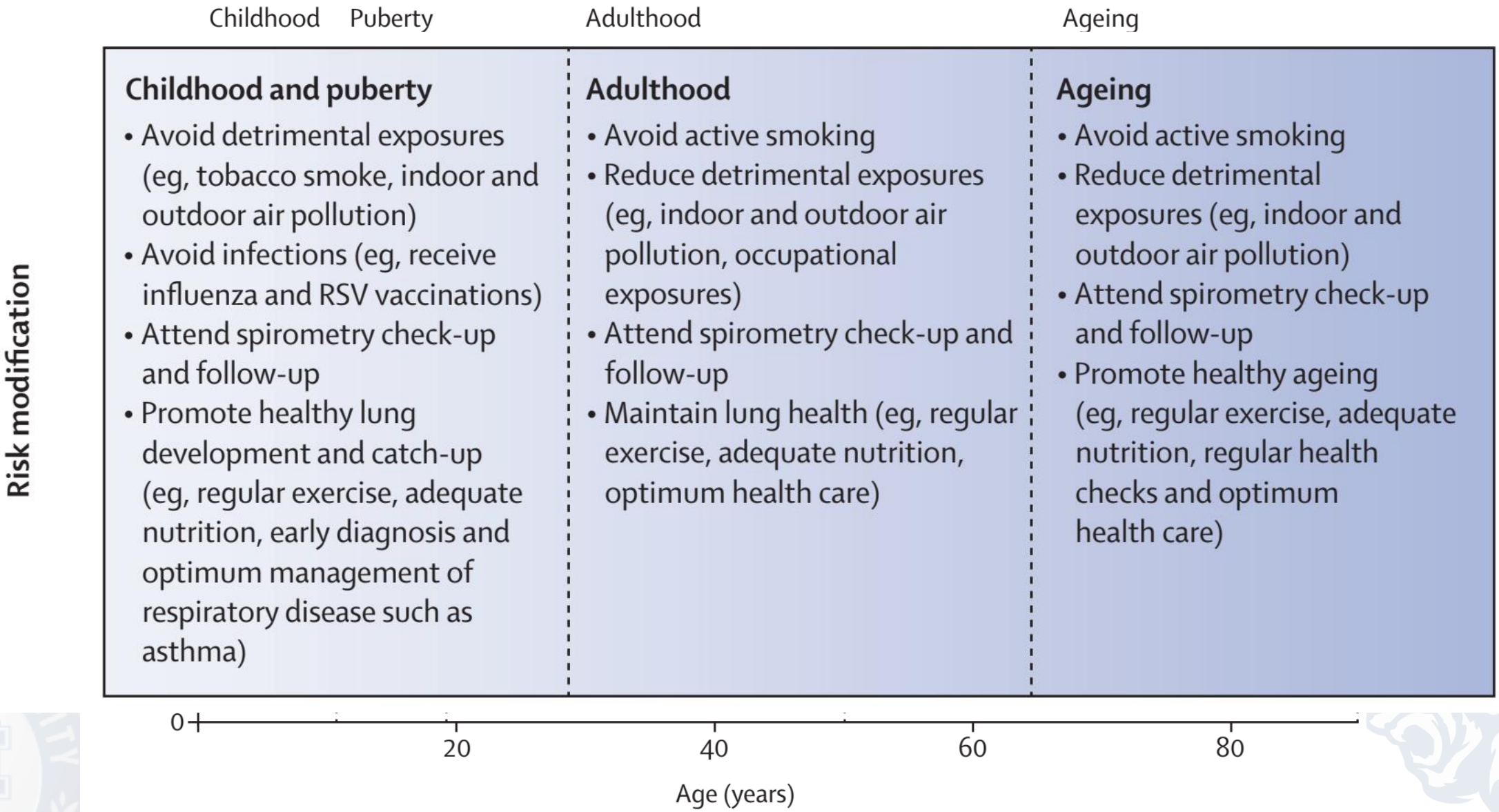
Agusti A et al. Lancet Respir Med 2022;10:512-24 [PMID 35427533]

Environmental and individual risk factors that affect lung function trajectories and lung health from before conception to old age



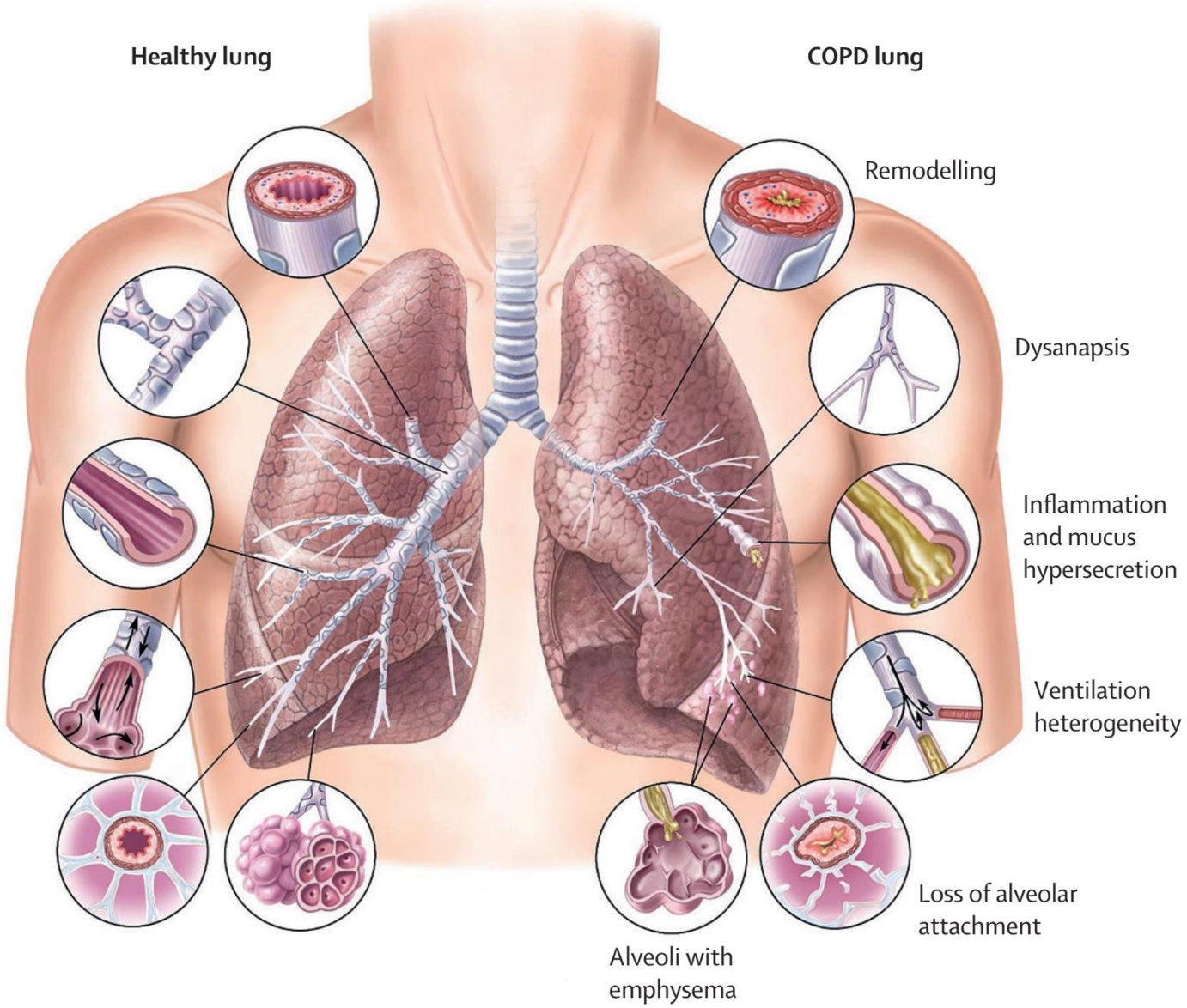
Stolz D et al. Lancet 2022;400:921-72 [PMID 36075255]

Potential lung function trajectories & opportunities for intervention



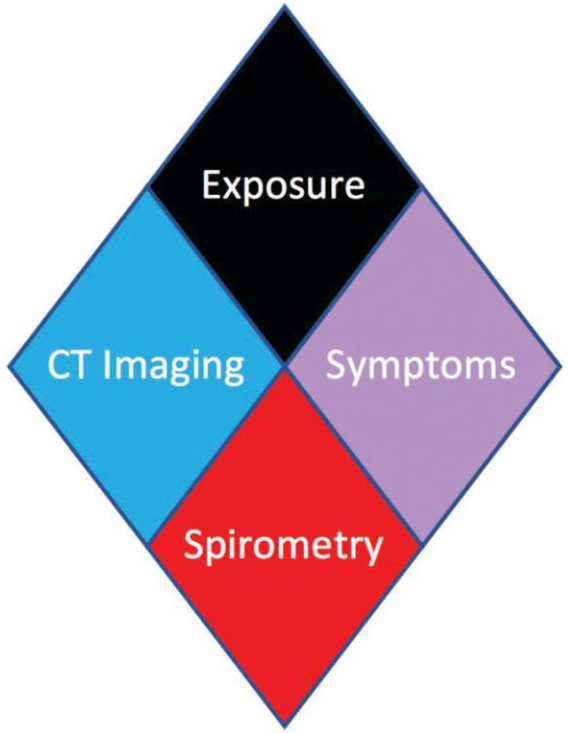
Agusti A et al. Lancet Respir Med 2022;10:512-24 [PMID 35427533]

Comparison of Physiology between Healthy Lungs and Lungs Affected by COPD

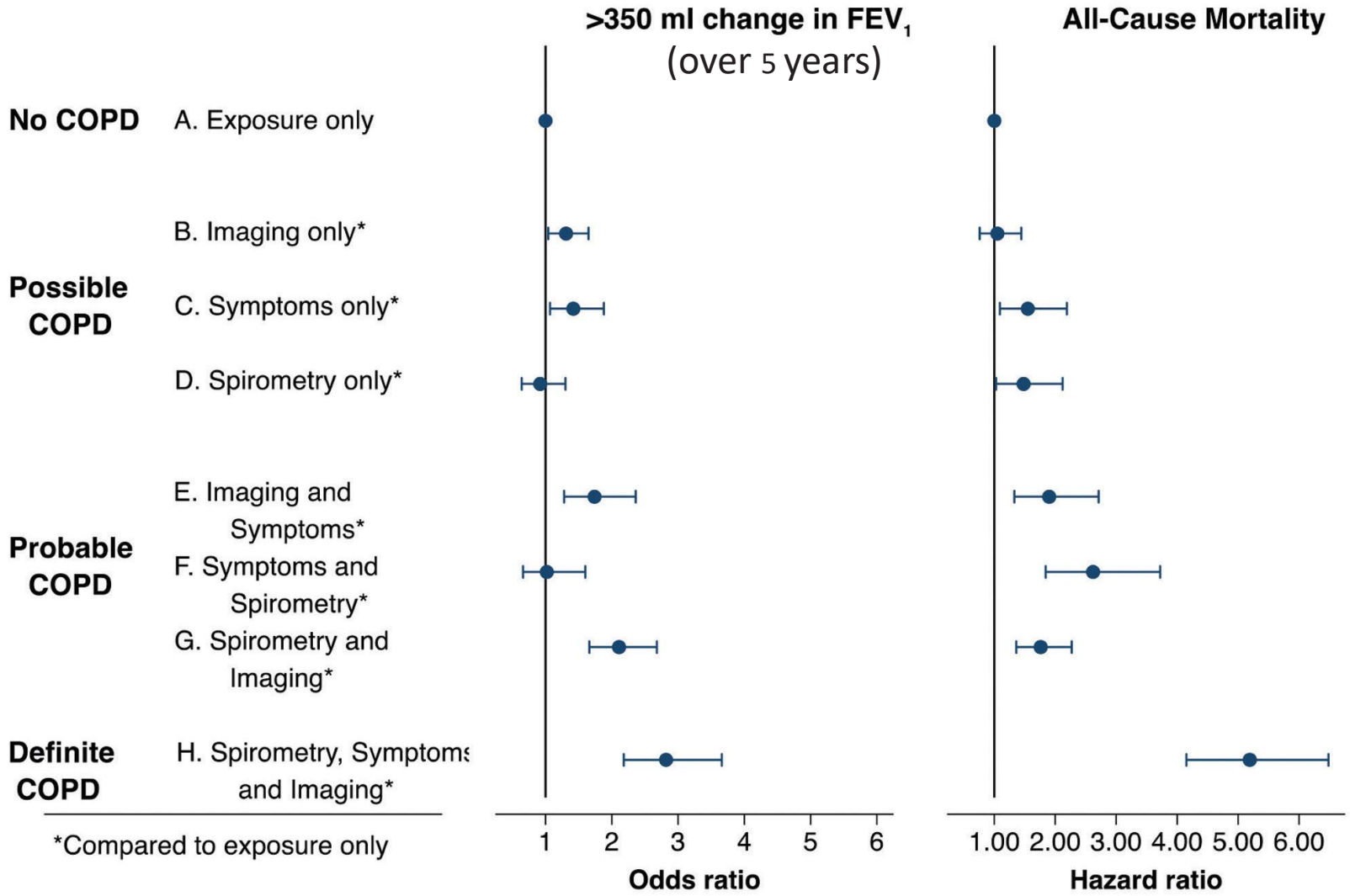


Stolz D et al. Lancet 2022;400:921-72 [PMID 36075255]

Forest Plot of Outcomes by COPDGene Categories

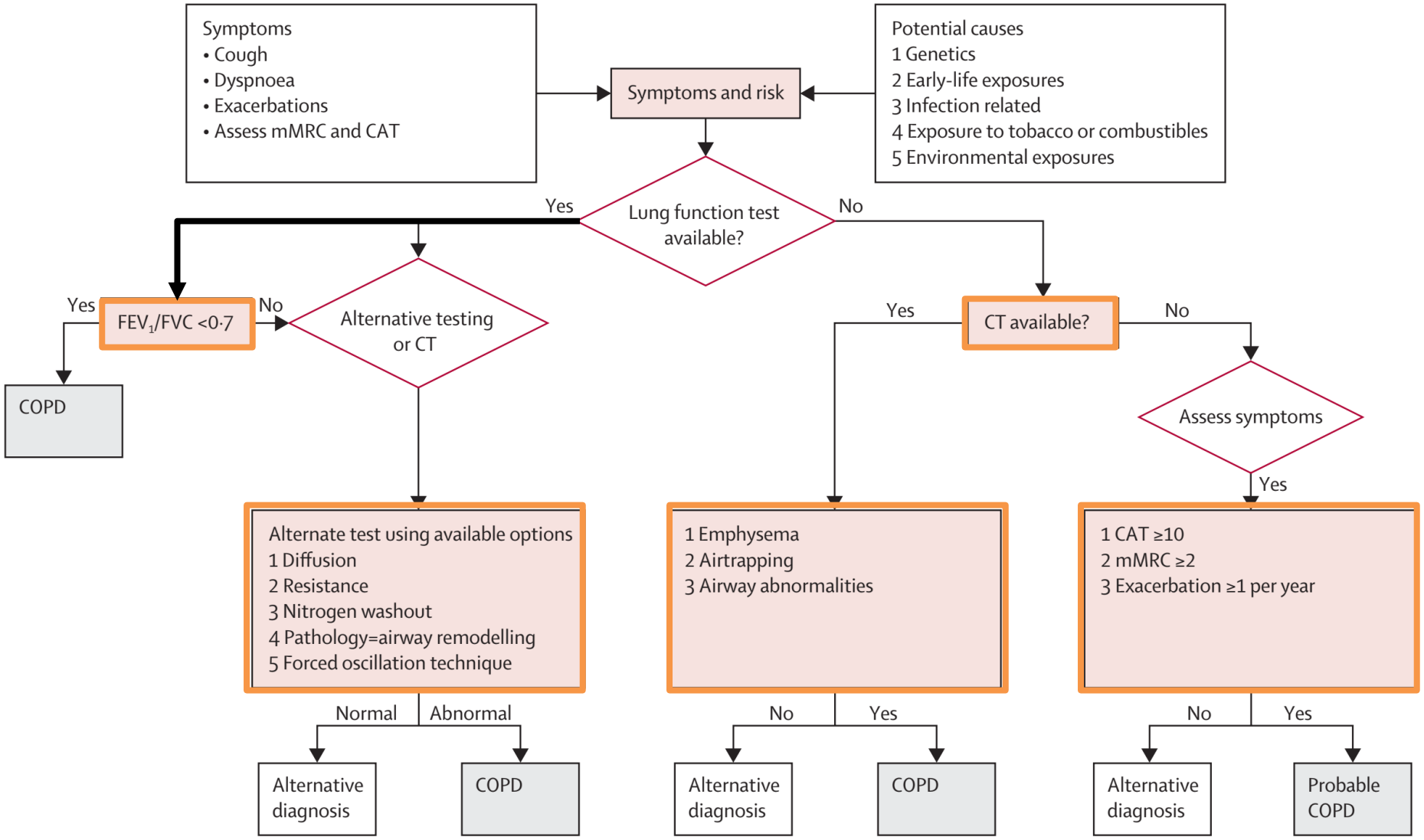


Exposure in the COPDGene® study includes individuals with a total of ≥ 10 pack years smoking. **CT Imaging** includes individuals with quantitative assessment showing ≥ 5% emphysema, a Pi10 ≥ 2.5 mm or ≥ 15% gas trapping. **Symptoms** include individuals with an mMRC dyspnea score ≥ 2 or chronic bronchitis. **Spirometry** includes individuals with FEV_1 < 80% predicted or FEV_1/FVC < 0.70.



Lowe KE et al. Chronic Obstr Pulm Dis 2019;6:384-99 [PMID 31710793]

Proposed Diagnostic Algorithm for COPD



Stolz D et al. Lancet 2022;400:921-72 [PMID 36075255]

putative mechanisms implicated in COPD in never-smokers

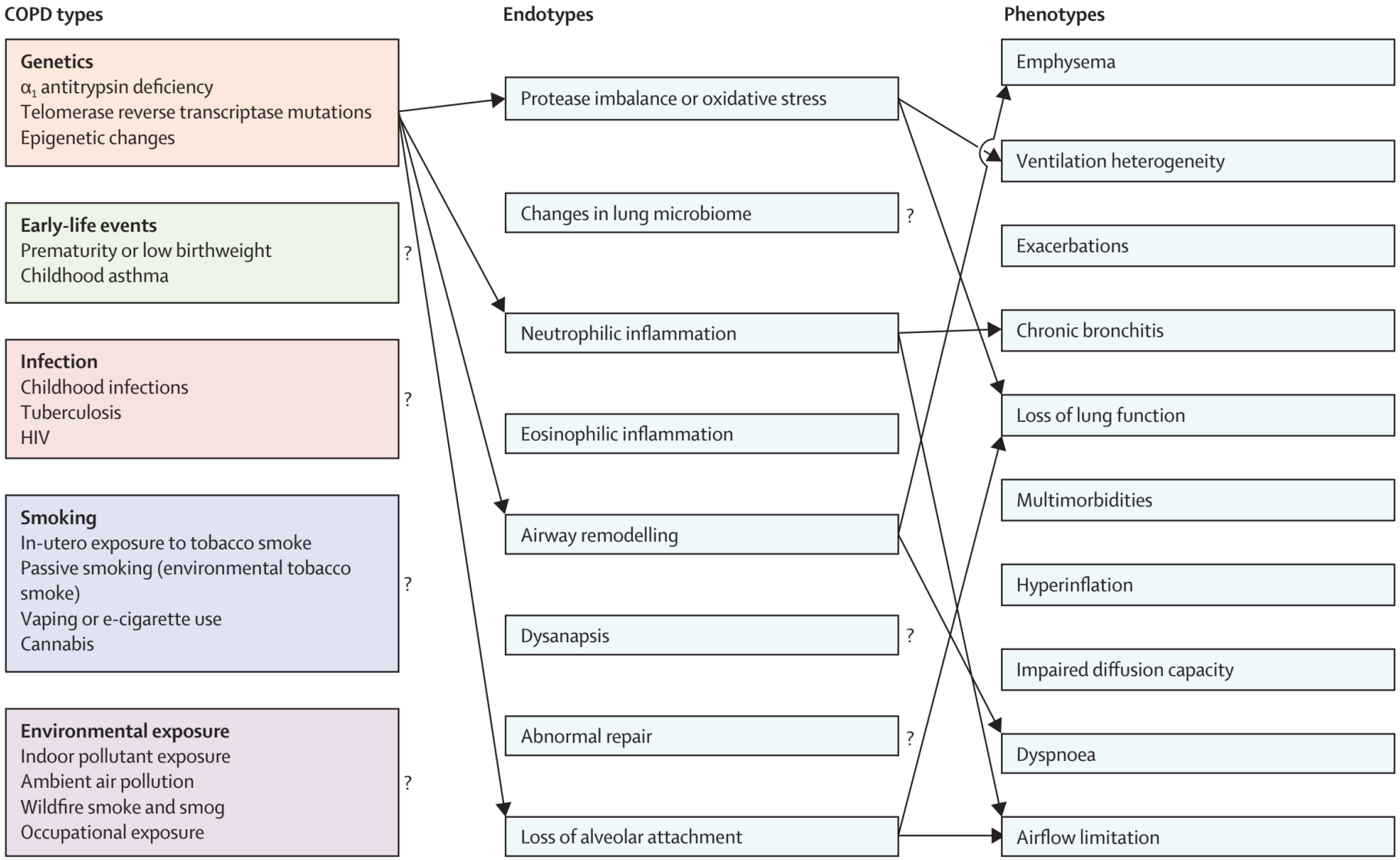
	Biomass smoke[37–39]	Asthma[40–42]	Occupational exposures[43]	Tuberculosis[44,45]	HIV[46–48]	Environmental tobacco smoke[49]	Impaired lung growth[50–52]
Pathways or pathology	Airway remodelling; oxidative stress; inflammation	Airway remodelling; bronchoconstriction; epithelial-to-mesenchymal transition	Inflammation	Tracheobronchial stenosis; small airway obstruction; bronchiolitis obliterans; matrix degradation	Altered immunity; respiratory infection; apoptosis; lung ageing	Inflammation; oxidative stress; epigenetics	Pathways and pathological features associated with various risk factors: maternal smoking; childhood respiratory infections and asthma; suboptimal nutrition; genetic factors
Cells, tissues, or structures involved	Bronchial epithelium; neutrophils; lymphocytes	Bronchial epithelium; smooth muscle; fibroblasts; goblet cells	Bronchial epithelium; monocytes; macrophages	Monocytes	Bronchial epithelium; $CD8^+$ lymphocytes; $CD4^+$ lymphocyte count	Bronchial epithelium; neutrophils; macrophages	Small airways and alveoli
Mediators	Cytokines; chemokines; MMP9, MMP12	Cytokines; TGF-β	Cytokines; adhesion molecules; pattern recognition receptors	Integrin αVβ3; MMP1, MMP10	MMP12; soluble CD14; reduced E-cadherin expression	Cytokines; p38 MAPK	Molecular and cellular responses to various in-utero and childhood exposures

A non-exhaustive list of potential mechanisms of action for risk factors for COPD in never-smokers identified in translational studies from the past 10 years. COPD=chronic obstructive pulmonary disease. MAPK=mitogen-activated protein kinase. MMP=matrix metalloproteinase. TGF-β=transforming growth factor-β.

Table 3: **Examples of putative mechanisms implicated in COPD in never-smokers**

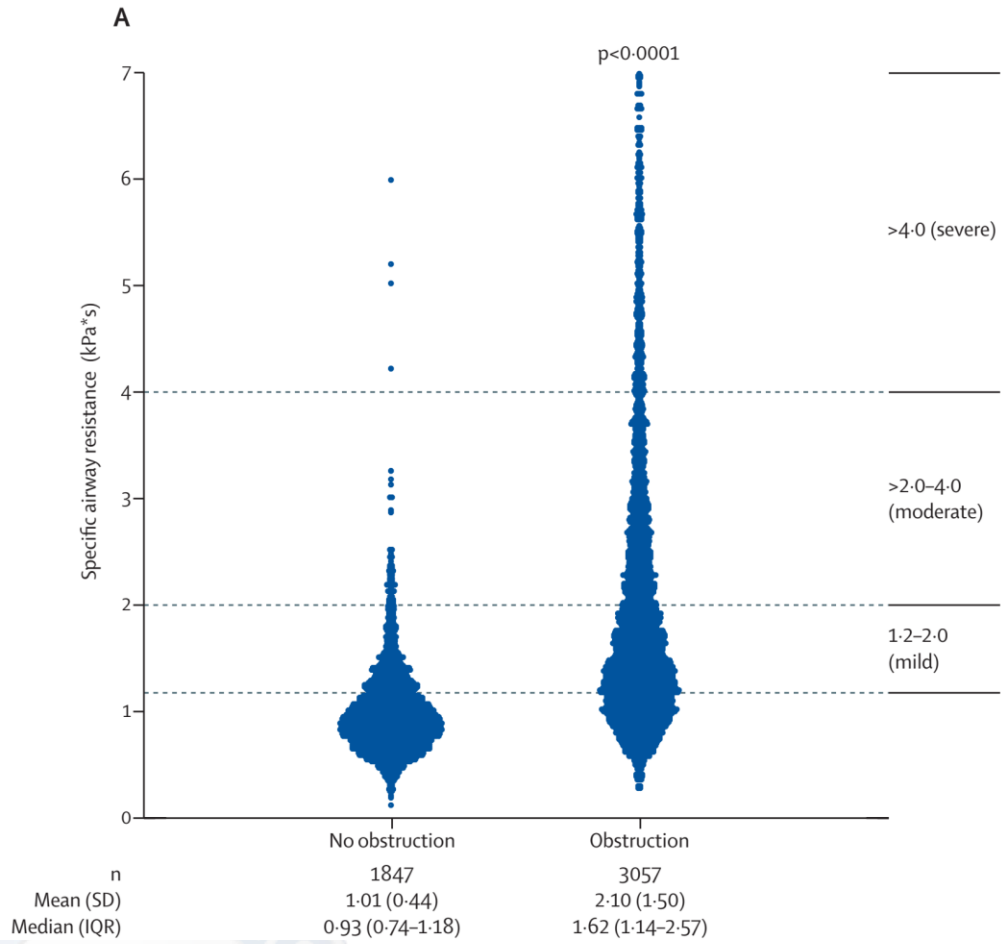
Yang IA. Chronic obstructive pulmonary disease in never-smokers: risk factors, pathogenesis, and implications for prevention and treatment. Lancet Respir Med 2022;10:497-511. [PMID 35427530]

Association between proposed COPD types, endotypes, and phenotypes



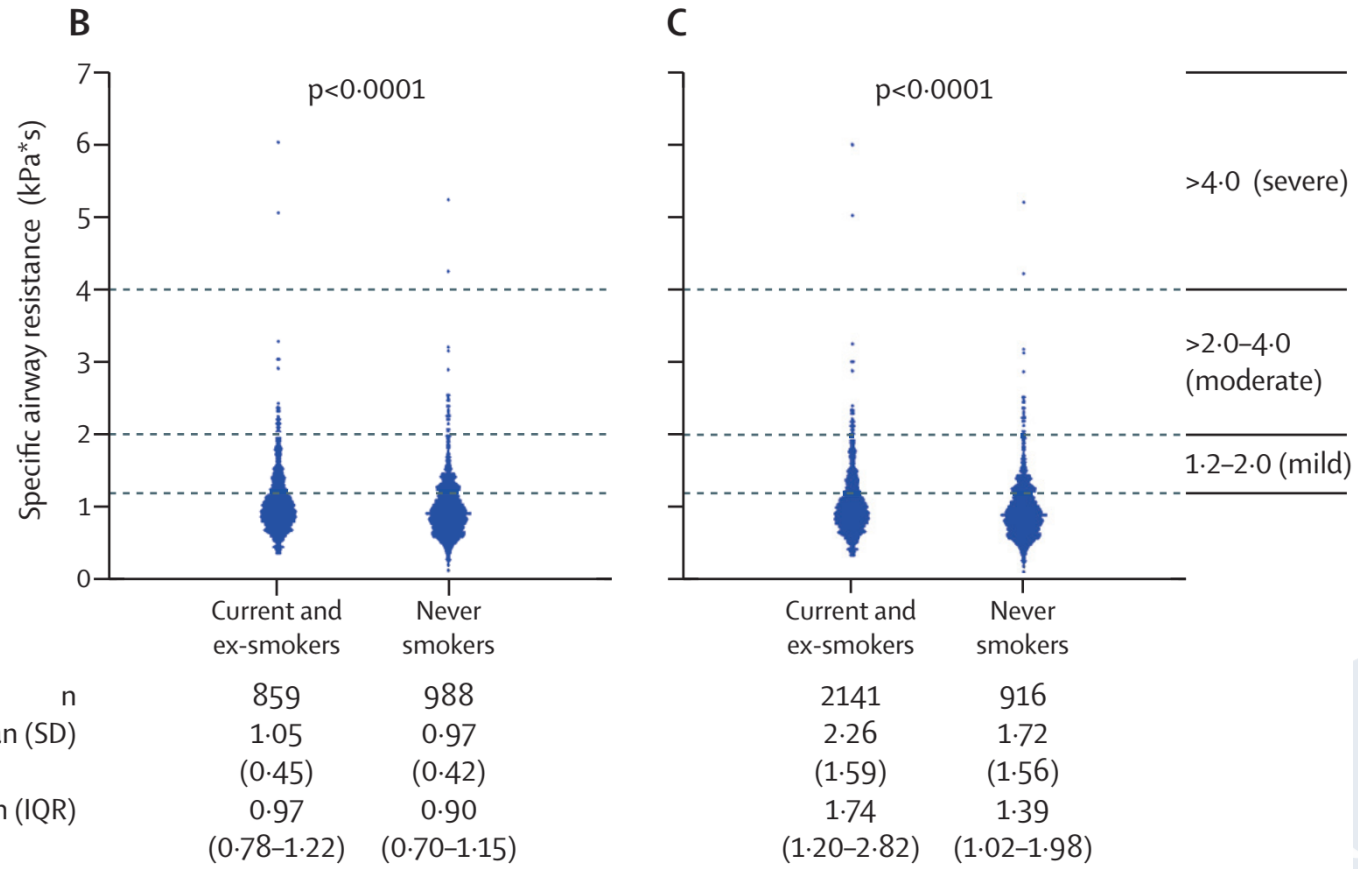
Stolz D et al. Lancet 2022;400:921-72 [PMID 36075255]

Specific effective airway resistance in different groups



without airflow limitation

with airflow limitation



Stolz D et al. Lancet 2022;400:921-72 [PMID 36075255]

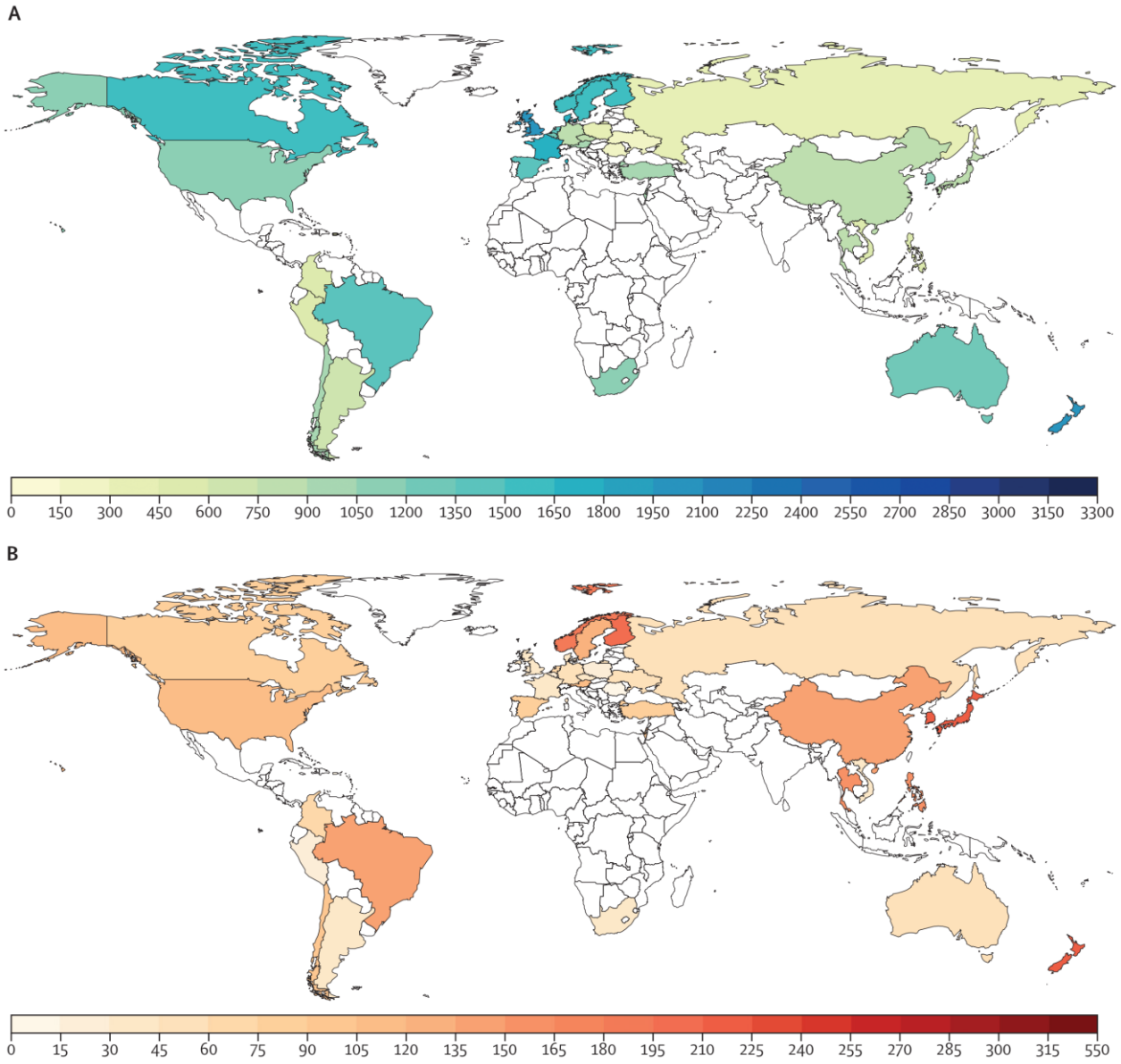
Ambiguity in Definition of COPD Exacerbation

	Ambiguity
Sustained	What duration of symptoms defines "sustained"?
Worsening	Which components of disease are getting worse?
Beyond	Occurring after how much time?
Acute	How quickly does a symptom have to emerge to be judged "acute"?
Might warrant	Does it require or not require treatment?

Table 4: **Ambiguous terms used to define exacerbations of chronic obstructive pulmonary disease**

Stolz D et al. Lancet 2022;400:921-72 [PMID 36075255]

Maps of the incidence of moderate or severe exacerbations (A) and pneumonia (B) (from the IMPACT study)



Stolz D et al. Lancet 2022;400:921-72 [PMID 36075255]

Suggested Definition of COPD exacerbations

- we suggest that an exacerbation should be defined as

  an increase in

  cough, dyspnoea, or sputum production and

  at least one of

  an increase in airflow limitation or ventilation heterogeneity,

  an increase in airway or systemic inflammation, or

  evidence of bacterial or viral infection,

  in the absence of evidence of

  acute cardiac ischaemia,

  congestive heart failure, or

  pulmonary embolism.

Stolz D et al. Lancet 2022;400:921-72 [PMID 36075255]

New diagnostic criteria for COPD exacerbations

	Essential	Dependent on context or presentation
Inflammation and infection		
Full blood count	X	
C-reactive protein or procalcitonin	X	
Airway microscopy and culture		X
Airway cytology (eosinophils)		X
Airway molecular testing for pathogens		X
Fractional exhaled nitric oxide		X
Hypoxia, hypercapnia, and metabolic status		
pH of venous blood gas		X
Arterial oxygen saturation	X	
General physiology		
Breathing rate	X	
Electrocardiography	X	
Lung function		X
Imaging		
Chest radiography, ultrasonography, or CT	X	
Systemic measurements		
D-dimer	X	
Renal function		X
Troponin		X
B-type natriuretic peptide		X

Table 5: **Standard investigations when patients with chronic obstructive pulmonary disease seek medical attention for suspected disease exacerbation**

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Panel 3: Classification criteria for severe exacerbations of chronic obstructive pulmonary disease

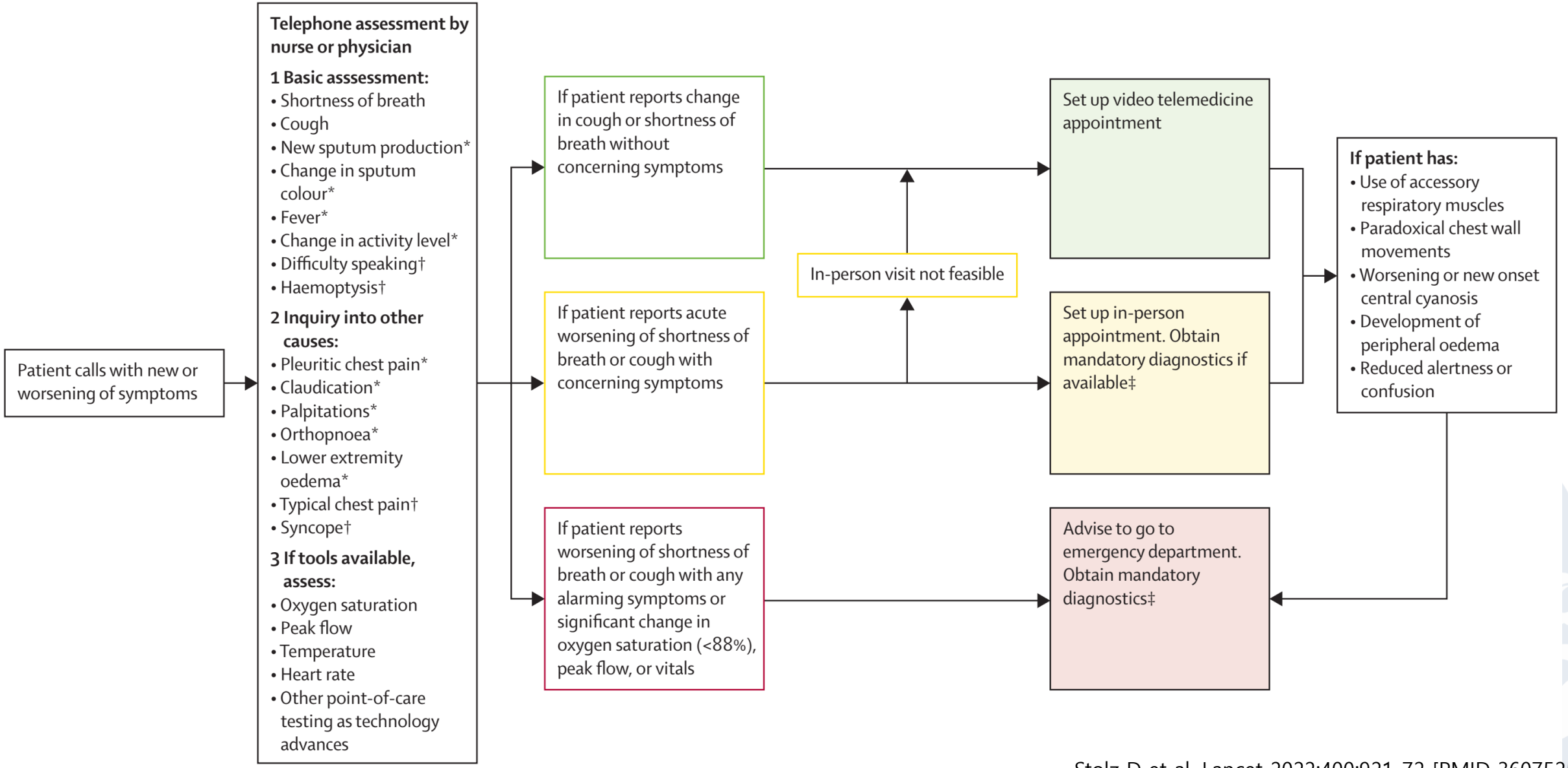
- Use of accessory respiratory muscles or paradoxical chest wall movements, or both
- Clinically significant hypoxaemia and new or worsening hypercapnia or respiratory acidosis
- Reduced alertness (eg, confusion, lethargy, coma)
- Failure to respond to initial medical management
- Right heart failure, cardiac ischaemia, haemodynamic instability, or clinically significant arrhythmia

The presence of any one of these criteria is sufficient to define an exacerbation as severe. A total severity score (range 1–5) can be calculated based on the total number of criteria that are met.

◆ The Commission proposes **to eliminate the definitions for mild or moderate exacerbations** and to instead diagnose only **severe** exacerbations or **non-severe** exacerbations.

Stolz D et al. Lancet 2022;400:921-72 [PMID 36075255]

Flowchart to assess the status of patients with COPD with new or worsening respiratory symptoms who contact medical personnel by telephone



Stolz D et al. Lancet 2022;400:921-72 [PMID 36075255]

Recommendations for the elimination of COPD

	Practical goals
Prohibit all kinds of smoking including—but not restricted to—cigarette smoking, water-pipe smoking, e-cigarette smoking (vaping), cannabis smoking, and smoking of other combustible substances	50% of countries to ban smoking by 2035
Eliminate environmental exposures to anything but clean air, including indoor and outdoor pollution, wildfire smoke, and occupational exposures to toxic fumes and gasses; regulatory authorities should strengthen legislation governing acceptable levels of exposure to inhalable particulate matter and ozone	50% of countries to introduce annual limits (lower than those recommended by WHO) for exposure to inhalable particulate matter <2·5 μm in diameter, particulate matter <10 μm in diameter, and ozone
Support measures associated with improved and sustained general health, including reductions in global poverty and improvements in nutrition, vaccination, prenatal care, physical activity, and mental health	At least a 50% reduction in people living below the poverty-line by 2035; all countries should provide free vaccinations and mobilise educational campaigns to inform at-risk individuals; free or low-cost health care for all
Diagnose COPD based on expanded criteria, including the presence of respiratory symptoms, personal history of risk factors, and persistent airflow limitation or ventilatory heterogeneity (as assessed by spirometry, other pulmonary function testing, or CT)	By 2035, the proportion of patients diagnosed with mild spirometric airflow obstruction should increase to at least 50% of the total
Research and development should focus on treatment of early disease	By 2030, 75% of published clinical trials should be focused on patients with early or mild disease
COPD should be classified into one of five types on the basis of the predominant risk factor present to increase awareness of risk factors, improve detection of people with non-smoking-related COPD and those with early disease, and foster research into therapies targeting specific disease mechanisms	COPD diagnosis by type should be included in the *International Classification of Diseases* coding system By 2035, at least one specific pharmacological or non-pharmacological therapy should be approved for each type of COPD

Stolz D et al. Lancet 2022;400:921-72 [PMID 36075255]

Recommendations for the elimination of COPD

Diagnosis of exacerbations should be based on a standard assessment confirmed by evidence of worsening airflow limitation or ventilatory heterogeneity, airways or systemic inflammation, or lung infection in a patient with increased respiratory symptoms (after exclusion of other disorders that mimic this presentation)	Exacerbation frequency should be similar worldwide by 2035 as a result of the establishment of a standard definition and assessment
Effective pharmacological and non-pharmacological therapies should be made available worldwide; development of new therapies should focus on underlying pathophysiology and take into account disease heterogeneity (including COPD type)	By 2035, at least 80% of patients with COPD should have disease control, as evidenced by the absence of respiratory symptoms and exacerbations and normal or near-normal quality of life, exercise capacity, and life expectancy
Definitions of treatment effectiveness should take patient-reported outcomes into account	By 2030, 75% of studies should include a patient-centred outcome as a primary outcome
Regulatory agencies should regularly revisit and update endpoints for clinical trials of treatments for different COPD types	By 2035, 75% of new therapies should be approved on the basis of non-spirometric criteria
Funding agencies should increase financial investments to adapt to the worldwide burden of COPD	By 2030, the total public and private global research and development expenditures for COPD should increase by 50%

COPD=chronic obstructive pulmonary disease.

Table 8: **Recommendations for the elimination of COPD**

Stolz D et al. Lancet 2022;400:921-72 [PMID 36075255]

Contents

CHAPTER 1: DEFINITION AND OVERVIEW

i. A new definition of COPD has been proposed (Page 5)

ii. Chapter 1 has been rewritten to incorporate new background information on COPD and new strategies for terminology and taxonomy

iii. A new section on Chronic Bronchitis has been added (Page 13)

Definition & Diagnostic Criteria of COPD in GOLD 2023

- **Definition**
  - Chronic Obstructive Pulmonary Disease (**COPD**) is a heterogeneous lung condition characterized by **chronic respiratory symptoms** (dyspnea, cough, sputum production) due to abnormalities of the **airways** (bronchitis, bronchiolitis) **and/or alveoli** (emphysema) that cause **persistent, often progressive, airflow obstruction**

- **Diagnostic** criteria
  - In the appropriate clinical context (See 'Definition' and 'Causes and Risk Factors' above), the presence of **non-fully reversible airflow limitation** (**FEV1/FVC < 0.7 post-bronchodilation**) measured by spirometry confirms the diagnosis of COPD.

Proposed Taxonomy (Etiotypes) for COPD

Classification	Description
Genetically determined COPD (COPD-G)	Alpha-1 antitrypsin deficiency (AATD) Other genetic variants with smaller effects acting in combination
COPD due to abnormal lung development (COPD-D)	Early life events, including premature birth and low birthweight, among others
Environmental COPD	
Cigarette smoking COPD (COPD-C)	• Exposure to tobacco smoke, including *in utero* or via passive smoking • Vaping or e-cigarette use • Cannabis
Biomass and pollution exposure COPD (COPD-P)	Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD due to infections (COPD-I)	Childhood infections, tuberculosis-associated COPD, WHIV-associated COPD
COPD & asthma (COPD-A)	Particularly childhood asthma
COPD of unknown cause (COPD-U)	

i. Defining early COPD, mild COPD, COPD in young people and pre-COPD (Page 12)

- **Early** COPD
  - The word "**early**" means "**near the beginning of a process**". Because COPD can start early in life and take a long time to manifest clinically, identifying "early" COPD is difficult. Further, **a biological "early"** related to the initial mechanisms that eventually lead to COPD should be differentiated from a **clinical "early",** which reflects the initial perception of symptoms, functional limitation and/or structural abnormalities noted. Thus, **we propose to use the term "early COPD" only to discuss "biological early",** when appropriate.
- **Mild** COPD.
  - Some studies have used "**mild**" airflow limitation as a surrogate for "**early**" disease.(128) This assumption is incorrect because not all patients started their journey from a **normal peak lung function** in early adulthood, so **some** of them may **never suffer "mild" disease** in terms of "severity" of airflow limitation.(104) Further, "**mild**" disease can **occur at any age** and may progress or not over time.(126) Accordingly**, we propose that "mild" should not be used to identify "early" COPD and *used only to describe the severity of airflow obstruction measured spirometrically*.**

GOLD 2023

i. Defining early COPD, mild COPD, COPD in young people and pre-COPD (Page 12)

- **Young COPD (**← COPD in **young** people. In GOLD 2022)
  - The term " young COPD" is seemingly straightforward because it directly relates to the **chronological age** of the subject. Given that lung function peaks at around 20-25 years,(56) **we propose to operationally consider "young COPD"** in patients aged **20–50 years.** (129)
  - Of note, this can include patients **who had never achieved normal peak lung function** in early adulthood and/or those with ***shorter plateau and/or*** early lung function decline.(130,131) ~~Young COPD may have a substantial impact on health and is~~ **frequently** ~~not diagnosed or treated.~~ Young COPD may be associated with structural and functional lung abnormalities.
  - (i.e., young COPD is not necessarily synonymous with "mild" COPD)
  - A **family history** of respiratory diseases and/or **early-life events** (including hospitalizations before the age of 5 years) is reported by a significant proportion of young people with COPD, further supporting the possibility of early-life origins of COPD.(127,131)

i. Defining early COPD, mild COPD, COPD in young people and pre-COPD (Page 12)

- **Pre-COPD**.
  - This term has been recently proposed to identify individuals (importantly, of any age) who have **respiratory symptoms** with or without detectable structural and/or functional abnormalities**, in the absence of airflow limitation.** These patients **may (or not) develop persistent airflow limitation** (i.e., COPD) over time.(132)
  - A very recent publication supports the need for RCTs, both in patients with pre-COPD, and in young people with COPD.(133)

Treatment Trials in Young Patients with Chronic Obstructive Pulmonary Disease and Pre–Chronic Obstructive Pulmonary Disease Patients

Time to Move Forward

Fernando J. Martinez[1*‡], Alvar Agusti[2,3,4,5*], Bartolome R. Celli[6*], MeiLan K. Han[7], James P. Allinson[8‡], Surya P. Bhatt[9], Peter Calverley[10‡], Sanjay H. Chotirmall[11‡], Badrul Chowdhury[12], Patrick Darken[13], Carla A. Da Silva[14], Gavin Donaldson[8‡], Paul Dorinsky[13], Mark Dransfield[9], Rosa Faner[15], David M. Halpin[16], Paul Jones[17], Jerry A. Krishnan[18‡], Nicholas Locantore[19], Fernando D. Martinez[20‡], Hana Mullerova[21], David Price[22,23], Klaus F. Rabe[24,25‡], Colin Reisner[26], Dave Singh[27], Jørgen Vestbo[28], Claus F. Vogelmeier[29], Robert A. Wise[30], Ruth Tal-Singer[31‖], and Jadwiga A. Wedzicha[8‖‡]

Table 2. Historical Factors Complicating Randomized Controlled Trials in COPD

1. Definition of the disease and its severity has been primarily focused on a single parameter (spirometry)
2. The paucity of regulatory accepted "qualified" intermediate efficacy endpoints and validated biomarkers
3. The nonnormal distribution of important trial outcomes
4. Differing patterns of disease progression
5. Slow FEV_1 decline, which is further compounded by dropout or death among the sickest
6. Disease heterogeneity: described as different phenotypes and endotypes (e.g., emphysema, airways disease, lung microbiome, neutrophilic vs. eosinophilic inflammation, aberrant tissue repair)
7. Variability of endpoints and their confounders (e.g., washout of background medications, diurnal variation, seasonal effect)

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

Martinez FJ et al. Am J Respir Crit Care Med 2022;205:275-87 [PMID 34672872]

Table 5. Future Steps in the Design and Conduct of Intervention Studies of Young Patients with COPD or Those at Risk with Pre-COPD

	Young Patients with COPD	Pre-COPD
Potential outcomes to explore	• Rate of FEV_1 decline • Time to first COPD exacerbation	• Time to onset of COPD • Time to worsening in CAT (1 point) or SGRQ (4 points)
Study duration	• 3 yr	• 3–5 yr
Interim analysis at 6–12 mo (to assess dropping therapy arms and/or extending trial duration/ increase sample size)	• Rate of FEV_1 decline • Time to first COPD exacerbation • CAT change • Composite outcomes*	• Rate of FEV_1 decline • CAT change • E-RS: COPD • Others (impulse oscillometry and/or lung imaging: airways disease parameters; HCRU events; CompEx COPD) • Composite outcomes*
Potential intervention arms	Currently approved medications for COPD	Currently approved medications for COPD as well as novel agents capable of modifying disease progression
Placebo control	No (as these are currently approved medications for airflow limitation with no age limits)	Yes (as these medications are not approved for this indication)
Study population as per the definition in the text (plus some other potential characteristics to consider in the study design to enrich the population studied)	• CAT score >10 • A respiratory HCRU event in 2 of the past 3 yr • Biomarker enrichment†	• Individuals with NOCB symptoms as defined using the CAT or SGRQ • A respiratory HCRU event in the past 24 mo • Subjects with rapid FEV_1 decline • Biomarker enrichment†

Definition of abbreviations: CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; E-RS = Evaluating Respiratory Symptoms in COPD tool; HCRU = health care resource utilization; NOCB = nonobstructive chronic bronchitis; SGRQ = St. George's Respiratory Questionnaire.

*Such as clinically important deterioration examining time to FEV_1 decline, exacerbation, or symptom worsening.

†Circulating eosinophils and microbial assessments (*see* the main text).

Martinez FJ et al. Am J Respir Crit Care Med 2022;205:275-87 [PMID 34672872]

i. Defining early COPD, mild COPD, COPD in young people and pre-COPD (Page 12)

- **PRISm**
  - This term describes individuals with preserved ratio (**FEV1/FVC ≥ 0.7 after bronchodilation**) but impaired spirometry (**FEV1 < 80% of reference, after bronchodilation**).(6,134) The prevalence of PRISm in population-based studies ranges from 7.1% to 20.3%,(134) and is particularly high in current and former smokers, and associated with both high and low body mass index values.(134) PRISm is associated with **increased all-cause mortality**. PRISm is **not always a stable phenotype** and can transition to both normal and obstructed spirometry over time.(134) Despite an increasing body of literature on PRISm, significant knowledge gaps remain in relation to its pathogenesis and treatment.(134)
  - **Not all individuals with pre-COPD or PRISm will eventually develop fixed airflow obstruction over time** (and hence COPD) but they should be considered "**patients**" (because they already suffer symptoms and/or have functional and/or structural abnormalities) and, as such, they deserve care and treatment. The challenge is that there is **no evidence on what the best treatment is for these patients yet**.(135) This is an important gap that deserves research.

CHAPTER 2: DIAGNOSIS AND INITIAL ASSESSMENT

iv. Additional information on **Screening and Case-Finding** has been included (Page 36)

v. The ABCD Assessment Tool has been revised to the **ABE Assessment Tool** to recognize the clinical relevance of exacerbations, independent of the level of symptoms (Page 115)

vi. New information on Imaging and Computed Tomography (**CT**) has been included (Page 43)

2023
Teaching
Slide Set

KEY INDICATORS FOR CONSIDERING A DIAGNOSIS OF COPD

Consider COPD, and perform spirometry, if any of these indicators are present in an individual over age 40. These indicators are not diagnostic themselves, but the presence of multiple key indicators increases the probability of a diagnosis of COPD. Spirometry is required to establish a diagnosis of COPD.

Dyspnea that is:	Progressive over time. Characteristically worse with exercise. Persistent.
Chronic Cough:	May be intermittent and may be unproductive. Recurrent wheeze.
Chronic Sputum Production:	Any pattern of chronic sputum production may indicate COPD.
Recurrent Lower Respiratory Tract Infections	
History of Risk Factors:	Host factors (such as genetic factors, congenital/developmental abnormalities etc.). Tobacco smoke (including popular local preparations). Smoke from home cooking and heating fuels. Occupational dusts, vapors, fumes, gases and other chemicals.
Family History of COPD and/or Childhood Factors:	For example low birthweight, childhood respiratory infections etc.

TABLE 2.1

Clinical Indicators for Considering a Diagnosis of COPD

Table 2.1

Consider the diagnosis of COPD, and perform spirometry, if any of these clinical indicators are present:
(these indicators are not diagnostic themselves, but the presence of multiple key indicators increases the probability of the presence of COPD; in any case, spirometry is required to establish a diagnosis of COPD)

Dyspnea that is	Progressive over time Worse with exercise Persistent
Recurrent wheeze	
Chronic cough	May be intermittent and may be unproductive
Recurrent lower respiratory tract infections	
History of risk factors	Tobacco smoke (including popular local preparations) Smoke from home cooking and heating fuels Occupational dusts, vapors, fumes, gases and other chemicals Host factors (e.g., genetic factors, developmental abnormalities, low birthweight, prematurity, childhood respiratory infections etc.)

DIFFERENTIAL DIAGNOSIS OF COPD

DIAGNOSIS	SUGGESTIVE FEATURES
COPD	Onset in mid-life. Symptoms slowly progressive. History of tobacco smoking or exposure to other types of smoke.
Asthma	Onset early in life (often childhood). Symptoms vary widely from day to day. Symptoms worse at night/early morning. Allergy, rhinitis, and/or eczema also present. Family history of asthma. Obesity coexistence.
Congestive Heart Failure	Chest X-ray shows dilated heart, pulmonary edema. Pulmonary function tests indicate volume restriction, not airflow limitation.
Bronchiectasis	Large volumes of purulent sputum. Commonly associated with bacterial infection. Chest X-ray/CT shows bronchial dilation, bronchial wall thickening.
Tuberculosis	Onset all ages. Chest X-ray shows lung infiltrate. Microbiological confirmation. High local prevalence of tuberculosis.
Obliterative Bronchiolitis	Onset at younger age, nonsmokers. May have history of rheumatoid arthritis or acute fume exposure. Seen after lung or bone marrow transplantation. CT on expiration shows hypodense areas.
Diffuse Panbronchiolitis	Predominantly seen in patients of Asian descent. Most patients are male and nonsmokers. Almost all have chronic sinusitis. Chest X-ray & HRCT show diffuse small centrilobular nodular opacities & hyperinflation.

These features tend to be characteristic of the respective diseases, but are not mandatory. For example, a person who has never smoked may develop COPD (especially in the developing world where other risk factors may be more important than cigarette smoking); asthma may develop in adult and even in elderly patients.

Differential Diagnosis of COPD

Table 2.3

Diagnosis	Suggestive Features
COPD	Symptoms slowly progressive History of tobacco smoking or other risk factors
Asthma	Variable airflow obstruction Symptoms vary widely from day to day Symptoms worse at night/early morning Allergy, rhinitis, and/or eczema also present Often occurs in children Family history of asthma
Congestive heart failure	Chest X-ray shows dilated heart, pulmonary edema Pulmonary function tests indicate volume restriction, not airflow obstruction
Bronchiectasis	Large volumes of purulent sputum Commonly associated with bacterial infection Chest X-ray/HRCT shows bronchial dilation
Tuberculosis	Onset all ages Chest X-ray shows lung infiltrate Microbiological confirmation High local prevalence of tuberculosis
Obliterative bronchiolitis	Can occur in children Seen after lung or bone marrow transplantation HRCT on expiration shows hypodense areas
Diffuse panbronchiolitis	Predominantly seen in patients of Asian descent Most patients are male and nonsmokers Almost all have chronic sinusitis Chest X-ray & HRCT show diffuse small centrilobular nodular opacities & hyperinflation

These features tend to be characteristic of the respective diseases, but are not mandatory. For example, a person who has never smoked may develop COPD (especially in LMICs where other risk factors may be more important than cigarette smoking).

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THE REFINED ABCD ASSESSMENT TOOL

Spirometrically Confirmed Diagnosis → Assessment of airflow limitation → Assessment of symptoms/risk of exacerbations

Post-bronchodilator $FEV_1/FVC < 0.7$

Grade	FEV_1 (% predicted)
GOLD 1	≥ 80
GOLD 2	50-79
GOLD 3	30-49
GOLD 4	< 30

Moderate or Severe Exacerbation History

- ≥2 or ≥ 1 leading to hospital admission
- 0 or 1 (not leading to hospital admission)

C	D
A	B

mMRC 0-1 CAT < 10 | mMRC ≥ 2 CAT ≥ 10

Symptoms

GOLD ABE Assessment Tool

Figure 2.3

Spirometrically confirmed diagnosis → Assessment of airflow obstruction → Assessment of symptoms/risk of exacerbations

Post-bronchodilator FEV1/FVC < 0.7

GRADE	FEV1 (% predicted)
GOLD 1	≥ 80
GOLD 2	50-79
GOLD 3	30-49
GOLD 4	< 30

EXACERBATION HISTORY

- ≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization
- 0 or 1 moderate exacerbations (not leading to hospitalization)

E	
A	B

mMRC 0-1 CAT < 10 | mMRC ≥ 2 CAT ≥ 10

SYMPTOMS

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Use of CT in Stable COPD

Table 2.8

Differential Diagnosis	• Frequent exacerbations with excessive cough with sputum production, raising concern for bronchiectasis or atypical infection • Symptoms out of proportion to disease severity based on lung function testing
Lung Volume Reduction	• Endobronchial valve therapy may be a therapeutic option for patients if they demonstrate postbronchodilator FEV1 between 15-45% and evidence of hyperinflation • Lung volume reduction surgery may be a therapeutic option for patients with hyperinflation, severe upper lobe predominant emphysema and low exercise capacity after pulmonary rehabilitation
Lung Cancer Screening	• Annual low-dose CT scan is recommended for lung cancer screening in patients with COPD due to smoking according to recommendations for the general population

CHAPTER 3: EVIDENCE SUPPORTING PREVENTION AND MAINTENANCE THERAPY

vii. **Vaccination** Recommendations for people with COPD have been updated in line with current guidance from the CDC (Page 54)

viii. Further information on **Therapeutic Interventions to Reduce COPD Mortality** and a new table has been included (Page 67)

ix. A new definition of COPD Exacerbation and a new set of parameters to assess exacerbation severity at the point of care has been included (Page 134)

x. Issues Related to **Inhaled Delivery** have been addressed (Page 69)

xi. Information on the topic of **Adherence** to Inhaled COPD Medications has been included (Page 71)

xii. A section on **Tele-rehabilitation** has been added (Page 76)

xiii. The section on **Interventional & Surgical Therapies for COPD** has been expanded (Page 82)

BRONCHODILATORS IN STABLE COPD

- Inhaled bronchodilators in COPD are central to symptom management and commonly given on a regular basis to prevent or reduce symptoms **(Evidence A)**.
- Regular and as-needed use of SABA or SAMA improves FEV_1 and symptoms **(Evidence A)**.
- Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV_1 and symptoms **(Evidence A)**.
- LABAs and LAMAs significantly improve lung function, dyspnea, health status, and reduce exacerbation rates **(Evidence A)**.
- LAMAs have a greater effect on exacerbation reduction compared with LABAs **(Evidence A)** and decrease hospitalizations **(Evidence B)**.
- Combination treatment with a LABA and LAMA increases FEV_1 and reduces symptoms compared to monotherapy **(Evidence A)**.
- Combination treatment with a LABA/LAMA reduces exacerbations compared to monotherapy **(Evidence B)**.
- Tiotropium improves the effectiveness of pulmonary rehabilitation in increasing exercise performance **(Evidence B)**.
- Theophylline exerts a small bronchodilator effect in stable COPD **(Evidence A)** and that is associated with modest symptomatic benefits **(Evidence B)**.

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Bronchodilators in Stable COPD

Table 3.4

- Inhaled bronchodilators in COPD are central to symptom management and commonly given on a regular basis to prevent or reduce symptoms **(Evidence A)**
- Regular and as-needed use of SABA or SAMA improves FEV1 and symptoms **(Evidence A)**
- Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV1 and symptoms **(Evidence A)**
- LABAs and LAMAs significantly improve lung function, dyspnea, health status, and reduce exacerbation rates **(Evidence A)**
- LAMAs have a greater effect on exacerbation reduction compared with LABAs **(Evidence A)** and decrease hospitalizations **(Evidence B)**
- Combination treatment with a LABA and a LAMA increases FEV1 and reduces symptoms compared to monotherapy **(Evidence A)**
- Combination treatment with a LABA+LAMA reduces exacerbations compared to monotherapy **(Evidence B)**
- Tiotropium improves the effectiveness of pulmonary rehabilitation in increasing exercise performance **(Evidence B)**
- Theophylline exerts a small bronchodilator effect in stable COPD **(Evidence A)** and that is associated with modest symptomatic benefits **(Evidence B)**
- Single inhaler therapy may be more convenient and effective than multiple inhalers

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ANTI-INFLAMMATORY THERAPY IN STABLE COPD

INHALED CORTICOSTEROIDS

- An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD **(Evidence A)**.
- Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease **(Evidence A)**.
- Triple inhaled therapy of LABA/LAMA/ICS improves lung function, symptoms and health status, and reduces exacerbations, compared to LABA/ICS, LABA/LAMA or LAMA monotherapy **(Evidence A)**. Recent data suggest a beneficial effect versus fixed-dose LABA/LAMA combinations on mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations.

ORAL GLUCOCORTICOIDS

- Long-term use of oral glucocorticoids has numerous side effects **(Evidence A)** with no evidence of benefits **(Evidence C)**.

PDE4 INHIBITORS

- In patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations:
  - » A PDE4 inhibitor improves lung function and reduces moderate and severe exacerbations **(Evidence A)**.
  - » A PDE4 inhibitor improves lung function and decreases exacerbations in patients who are on fixed-dose LABA/ICS combinations **(Evidence A)**.

ANTIBIOTICS

- Long-term azithromycin and erythromycin therapy reduces exacerbations over one year **(Evidence A)**.
- Treatment with azithromycin is associated with an increased incidence of bacterial resistance **(Evidence A)** and hearing test impairments **(Evidence B)**.

MUCOREGULATORS AND ANTIOXIDANT AGENTS

- Regular treatment with mucolytics such as erdosteine, carbocysteine and NAC reduces the risk of exacerbations in select populations **(Evidence B)**.

OTHER ANTI-INFLAMMATORY AGENTS

- Simvastatin does not prevent exacerbations in COPD patients at increased risk of exacerbations and without indications for statin therapy **(Evidence A)**. However, observational studies suggest that statins may have positive effects on some outcomes in patients with COPD who receive them for cardiovascular and metabolic indications **(Evidence C)**.
- Leukotriene modifiers have not been tested adequately in COPD patients.

Anti-Inflammatory Therapy in Stable COPD

Table 3.5

Inhaled Corticosteroids	• An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD **(Evidence A)** • Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease **(Evidence A)** • Lower blood and sputum eosinophils are associated with greater presence of proteobacteria, notably *Haemophilus*, increased bacterial infections & pneumonia • Independent of ICS use, there is evidence that a blood eosinophil count < 2% increases the risk of pneumonia **(Evidence C)** • Triple inhaled therapy of LABA+LAMA+ICS improves lung function, symptoms and health status, and reduces exacerbations, compared to LABA+ICS, LABA+LAMA or LAMA monotherapy **(Evidence A)**. Recent data suggest a beneficial effect of triple inhaled therapy versus fixed-dose LABA+LAMA combinations on mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations • Single inhaler therapy may be more convenient and effective than multiple inhaler
Oral Glucocorticoids	• Long-term use of oral glucocorticoids has numerous side effects **(Evidence A)** with no evidence of benefits **(Evidence C)**
PDE4 Inhibitors	• In patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations: ▪ A PDE4 inhibitor improves lung function and reduces moderate and severe exacerbations **(Evidence A)** ▪ A PDE4 inhibitor improves lung function and decreases exacerbations in patients who are on fixed-dose LABA+ICS combinations **(Evidence A)**
Antibiotics	• Long-term azithromycin and erythromycin therapy reduces exacerbations over one year **(Evidence A)** • Treatment with azithromycin is associated with an increased incidence of bacterial resistance **(Evidence A)** and hearing test impairments **(Evidence B)**
Mucoregulators and Antioxidant Agents	• Regular treatment with mucolytics such as erdosteine, carbocysteine and NAC reduces the risk of exacerbations in select populations **(Evidence B)**
Other Anti-Inflammatory Agents	• Simvastatin does not prevent exacerbations in COPD patients at increased risk of exacerbations and without indications for statin therapy **(Evidence A)**. However, observational studies suggest that statins may have positive effects on some outcomes in patients with COPD who receive them for cardiovascular and metabolic indications **(Evidence C)** • Leukotriene modifiers have not been tested adequately in COPD patients

Evidence Supporting a Reduction in Mortality with Pharmacotherapy and Non-pharmacotherapy in COPD Patients

Table 3.6

Therapy	RCT*	Treatment effect on mortality	Patient characteristics
Pharmacotherapy			
LABA+LAMA+ICS[1]	Yes	Triple compared to dual LABD relative risk reduction: IMPACT HR 0.72 (95% CI: 0.53, 0.99) ETHOS HR 0.51 (95% CI: 0.33, 0.80)	Symptomatic people with a history of frequent and/or severe exacerbations
Non-Pharmacological Therapy			
Smoking (Sm) Cessation[2]	Yes	8.83/1000 person-years (Sm cessation) vs 10.38/1000 person-years (UC) (p = 0.03)	Asymptomatic or mildly symptomatic
Pulmonary Rehabilitation (PR)[3]	Yes	After early PR: RR 0.58 (95% CI 0.35, 0.98) and at the longest follow-up RR 0.55 (95% CI 0.12, 2.57)	Hospitalized for exacerbations of COPD (during or ≤ 4 weeks post d/c)
LTOT[4]	Yes	NOTT, ≥ 19 hours of continuous oxygen vs ≤ 13 hours: 50% reduction MRC, ≥ 15 hours vs no oxygen: 50% reduction	PaO_2 ≤ 55 or < 60 mmHg with *cor pulmonale* or secondary polycythemia
NPPV[5]	Yes	12% in NPPV (high IPAP level) and 33% in control (HR 0.24; 95% CI 0.11, 0.49)	Stable COPD with marked hypercapnia
LVRS[6]	Yes	0.07 deaths/person-year (LVRS) vs 0.15 deaths/person-year (UC) RR for death 0.47 (p = 0.005)	Upper lobe emphysema and low exercise capacity

*RCT with pre-specified analysis of the mortality outcome (primary or secondary outcome)

1. IMPACT and ETHOS trials (Lipson et al. 2020; Martinez et al. 2021). 2.Lung Health Study (Anthonisen et al. 2005). 3. Review and meta-analysis (Ryrso et al. 2018) 4. NOTT and MRC trials (NOTT 1980; MRC 1981) 5. Kohlein et al., trial (Kohlein et al. 2014) 6. NETT trial (Fishman et al. 2003)

ICS: inhaled corticosteroid; LABA: long-acting B2-agonist; LAMA: long acting anti-muscarinic; LTOT: long-term oxygen therapy; NPPV: noninvasive positive pressure ventilation; LVRS: lung volume reduction surgery; UC: usual treatment control group.

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Overview of Current and Proposed Surgical and Bronchoscopic Interventions for People with COPD

Figure 3.2

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Symptoms	Chronic Mucus Production	Exacerbations	Dyspnea
Disorders	• Chronic bronchitis	• Acute and chronic bronchitis • Bulla • Emphysema • Tracheobronchomalcia	• Bulla • Emphysema • Tracheobronchomalcia
Surgical and Bronchoscopic Interventions	• Nitrogen cryospray • Rheoplasty	• Targeted lung denervation	• Giant bullectomy • Large airway stenting • EBV • Coil • Thermal vapor ablation • Lung sealants • LVRS • Lung transplantation

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INTERVENTIONAL THERAPY IN STABLE COPD

LUNG VOLUME REDUCTION SURGERY

- Lung volume reduction surgery improves survival in severe emphysema patients with an upper–lobe emphysema and low post–rehabilitation exercise capacity **(Evidence A)**.

BULLECTOMY

- In selected patients, bullectomy is associated with decreased dyspnea, improved lung function and exercise tolerance **(Evidence C)**.

TRANSPLANTATION

- In appropriately selected patients with very severe COPD, lung transplantation has been shown to improve quality of life and functional capacity **(Evidence C)**.

BRONCHOSCOPIC INTERVENTIONS

- In select patients with advanced emphysema, bronchoscopic interventions reduce end-expiratory lung volume and improve exercise tolerance, health status and lung function at 6-12 months following treatment. Endobronchial valves **(Evidence A)**; Lung coils **(Evidence B)**; Vapor ablation **(Evidence B)**.

Interventional Therapy in Stable COPD

Table 3.11

Lung Volume Reduction Surgery	• Lung volume reduction surgery improves survival in severe emphysema patients with an upper-lobe emphysema and low post-rehabilitation exercise capacity **(Evidence A)**
Bullectomy	• In selected patients, bullectomy is associated with decreased dyspnea, improved lung function and exercise tolerance **(Evidence C)**
Transplantation	• In appropriately selected patients with very severe COPD, lung transplantation has been shown to improve quality of life and functional capacity **(Evidence C)**
Bronchoscopic Interventions	• In select patients with advanced emphysema, bronchoscopic interventions reduce end-expiratory lung volume and improve exercise tolerance, health status and lung function at 6-12 months following treatment. Endobronchial valves **(Evidence A)**; Lung coils **(Evidence B)**; Vapor ablation **(Evidence B)**
Bronchoscopic Interventions Under Study	• Phase III trials are currently being conducted to determine the efficacy of treatments for patients with refractory exacerbations and chronic bronchitis using cryospray, rheoplasty and targeted lung denervation technology

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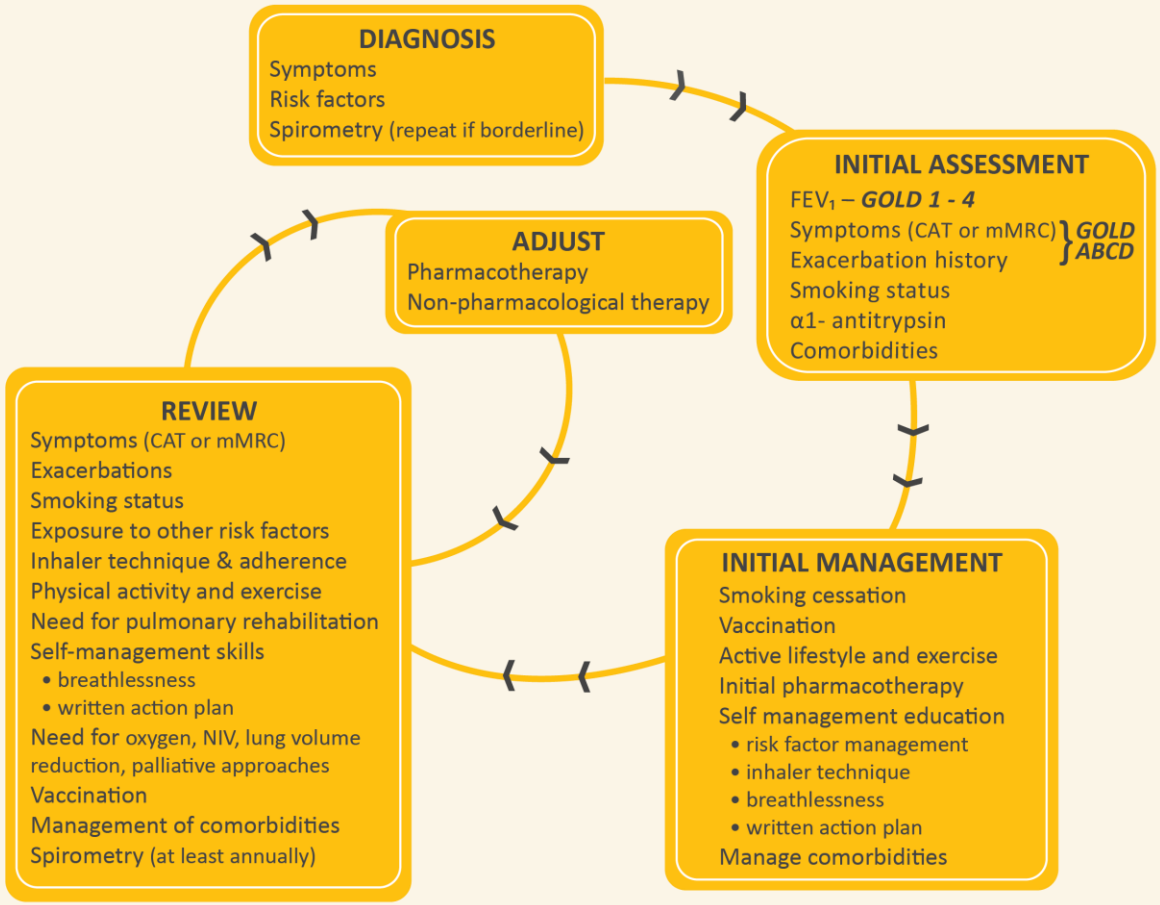
MANAGEMENT OF COPD



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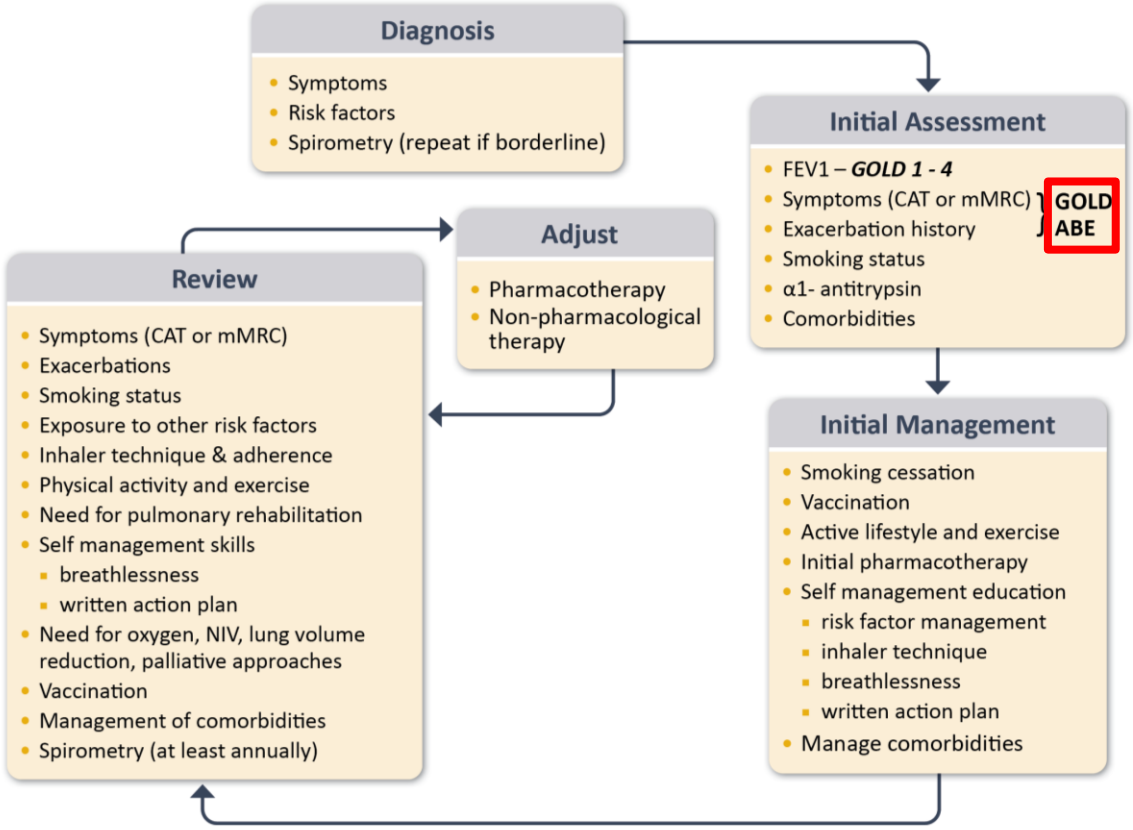
Management of COPD

Figure 4.1



CHAPTER 4: MANAGEMENT OF STABLE COPD

xiv. New information on the **Choice of Inhaler Device** and a new table has been added (Page 112)

xv. The information and figures outlining Initial Pharmacological Treatment and Follow-up Pharmacological Treatment have been updated. In particular, **the positioning of LABA+LAMA and of LABA+ICS has been changed** (Page 115)

KEY POINTS FOR INHALATION OF DRUGS

- The choice of inhaler device has to be individually tailored and will depend on access, cost, prescriber, and most importantly, patient's ability and preference.
- It is essential to provide instructions and to demonstrate the proper inhalation technique when prescribing a device, to ensure that inhaler technique is adequate and re-check at each visit that patients continue to use their inhaler correctly.
- Inhaler technique (and adherence to therapy) should be assessed before concluding that the current therapy requires modification.

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Key Points for Inhalation of Drugs

Table 4.4

- When a treatment is given by the inhaled route, the importance of education and training in inhaler device technique cannot be over-emphasized
- The choice of inhaler device has to be individually tailored and will depend on access, cost, prescriber, and most importantly, patient's ability and preference
- It is essential to provide instructions and to demonstrate the proper inhalation technique when prescribing a device, to ensure that inhaler technique is adequate and re-check at each visit that patients continue to use their inhaler correctly
- Inhaler technique (and adherence to therapy) should be assessed before concluding that the current therapy is insufficient

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Basic Principles for Appropriate Inhalation Device Choice

Table 4.5

- Availability of the drug in the device
- Patients' beliefs, satisfaction with current and previous devices and preferences need to be assessed and considered
- The number of different device types should be minimized for each patient. Ideally, only one device type should be used
- Device type should not be switched in the absence of clinical justification nor without proper information, education and medical follow-up
- Shared decision making is the most appropriate strategy for inhalation device choice
- Patient's cognition, dexterity and strength must be taken into account
- Patient's ability to perform the correct specific inhalation manoeuvre for the device must be assessed:
  - Dry powder inhalers are appropriate only if the patient can make a forceful and deep inhalation. Check visually that the patient can inhale forcefully through the device - if there is doubt assess objectively or chose alternative device
  - Metered-dose inhalers and, to a lesser extent, soft mist inhalers require coordination between device triggering and inhalation and patients need to be able to perform a slow and deep inhalation. Check visually that the patient can inhale slowly and deeply from the device - if there is doubt consider adding a spacer/ VHC or chose alternative device
  - For patients unable to use an MDI (with or without spacer/VHC), SMI or DPI a nebulizer should be considered
- Other factors to consider include size, portability, cost
- Smart inhalers may be useful if there are issues with adherence/persistence or inhalation technique (for devices that can check it)
- Physicians should prescribe only devices they (and the other members of the caring team) know how to use

KEY POINTS FOR THE USE OF ANTI-INFLAMMATORY AGENTS

- Long-term monotherapy with ICS is not recommended **(Evidence A)**.
- Long-term treatment with ICS may be considered in association with LABAs for patients with a history of exacerbations despite appropriate treatment with long-acting bronchodilators **(Evidence A)**.
- Long-term therapy with oral corticosteroids is not recommended **(Evidence A)**.
- In patients with severe to very severe airflow limitation, chronic bronchitis and exacerbations the addition of a PDE4 inhibitor to a treatment with long acting bronchodilators with/without ICS can be considered **(Evidence B)**.
- Preferentially, but not only in former smokers with exacerbations despite appropriate therapy, macrolides, in particular azithromycin, can be considered **(Evidence B)**.
- Statin therapy is not recommended for prevention of exacerbations **(Evidence A)**.
- Antioxidant mucolytics are recommended only in selected patients **(Evidence A)**.

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Key Points for the Use of Anti-Inflammatory Agents

Table 4.7

- Long-term monotherapy with ICS is not recommended **(Evidence A)**
- We do not encourage the use of a LABA+ICS combination in COPD. If there is an indication for an ICS the combination LABA+LAMA+ICS has been shown to be superior to LABA+ICS and is therefore the preferred choice. This combination can be given as single or multiple inhaler therapy.
- If patients with COPD have features of asthma, treatment should always contain an ICS
- In patients with severe to very severe airflow limitation, chronic bronchitis and exacerbations the addition of a PDE4 inhibitor to a treatment with long acting bronchodilators with/without ICS can be considered **(Evidence B)**
- Preferentially, but not only in former smokers with exacerbations despite appropriate therapy, macrolides, in particular azithromycin, can be considered **(Evidence B)**
- Statin therapy and/or beta-blockers are not recommended for prevention of exacerbations **(Evidence A)**

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INITIAL PHARMACOLOGICAL TREATMENT

≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization	**Group C** LAMA	**Group D** LAMA or LAMA + LABA* or ICS + LABA** *Consider if highly symptomatic (e.g. CAT > 20) **Consider if eos ≥ 300
0 or 1 moderate exacerbations (not leading to hospital admission)	**Group A** A Bronchodilator	**Group B** A Long Acting Bronchodilator (LABA or LAMA)
	mMRC 0-1, CAT < 10	mMRC ≥ 2, CAT ≥ 10

FIGURE 4.2

Initial Pharmacological Treatment

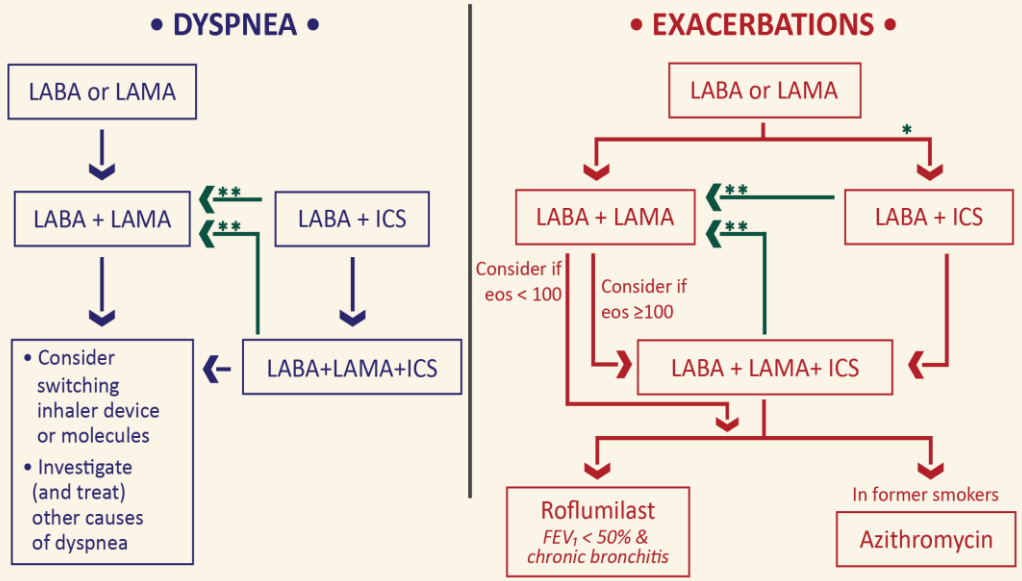
Figure 4.2

≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization	**GROUP E** **LABA + LAMA*** *consider LABA+LAMA+ICS* if blood eos ≥ 300*	
0 or 1 moderate exacerbations (not leading to hospital admission)	**GROUP A** **A bronchodilator**	**GROUP B** **LABA + LAMA***
	mMRC 0-1, CAT < 10	mMRC ≥ 2, CAT ≥ 10

*single inhaler therapy may be more convenient and effective than multiple inhalers

FOLLOW-UP PHARMACOLOGICAL TREATMENT

1. IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.
2. IF NOT:
   - ✓ Consider the predominant treatable trait to target (dyspnea or exacerbations)
     - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   - ✓ Place patient in box corresponding to current treatment & follow indications
   - ✓ Assess response, adjust and review
   - ✓ These recommendations do not depend on the ABCD assessment at diagnosis



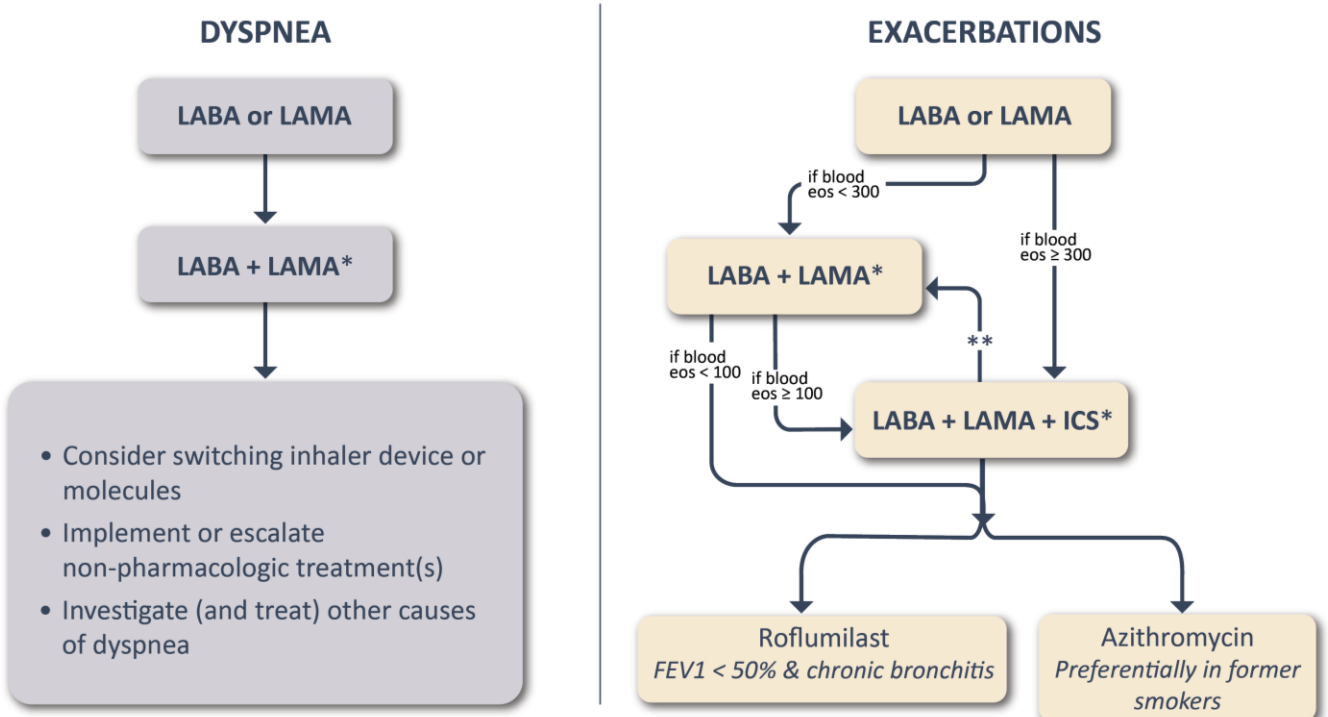
eos = blood eosinophil count (cells/μL)
** Consider if eos ≥ 300 or eos ≥ 100 AND ≥2 moderate exacerbations / 1 hospitalization*
*** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS*

FIGURE 4.4

Follow-up Pharmacological Treatment

Figure 4.4

1. IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.
2. IF NOT:
   - Check adherence, inhaler technique and possible interfering comorbidities
   - Consider the predominant treatable trait to target (dyspnea or exacerbations)
     - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   - Place patient in box corresponding to current treatment & follow indications
   - Assess response, adjust and review
   - These recommendations do not depend on the ABE assessment at diagnosis



*Single inhaler therapy may be more convenient and effective than multiple inhalers

**Consider de-escalation of ICS if pneumonia or other considerable side-effects. In case of blood eos ≥ 300 cells/μl de-escalation is more likely to be associated with the development of exacerbations

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 Pertussis Vaccination Covid-19 Vaccination
B, C and D	Smoking Cessation (can include pharmacologic treatment) Pulmonary Rehabilitation	Physical Activity	Flu Vaccination Pneumococcal Vaccination Pertussis Vaccination Covid-19 Vaccination

*Can include pharmacologic treatment.

TABLE 4.8

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Non-Pharmacologic Management of COPD*

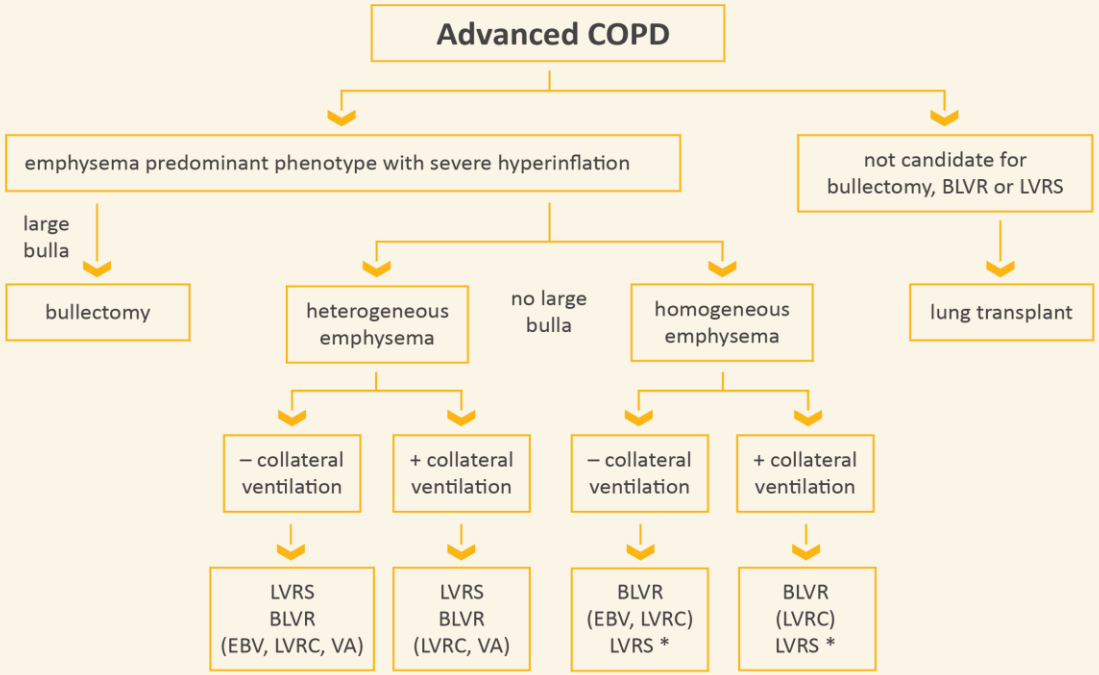
Table 4.9

Patient Group	Essential	Recommended	Depending on Local Guidelines
A	Smoking Cessation (can include pharmacological treatment)	Physical Activity	Flu Vaccination Pneumococcal Vaccination Pertussis Vaccination COVID-19 Vaccinations Shingles Vaccination
B and E	Smoking Cessation (can include pharmacological treatment) Pulmonary Rehabilitation	Physical Activity	Flu Vaccination Pneumococcal Vaccination Pertussis Vaccination COVID-19 Vaccinations Shingles Vaccination

*Can include pharmacologic treatment

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, VA, Vapor ablation

*at some but not all centers

FIGURE 4.6

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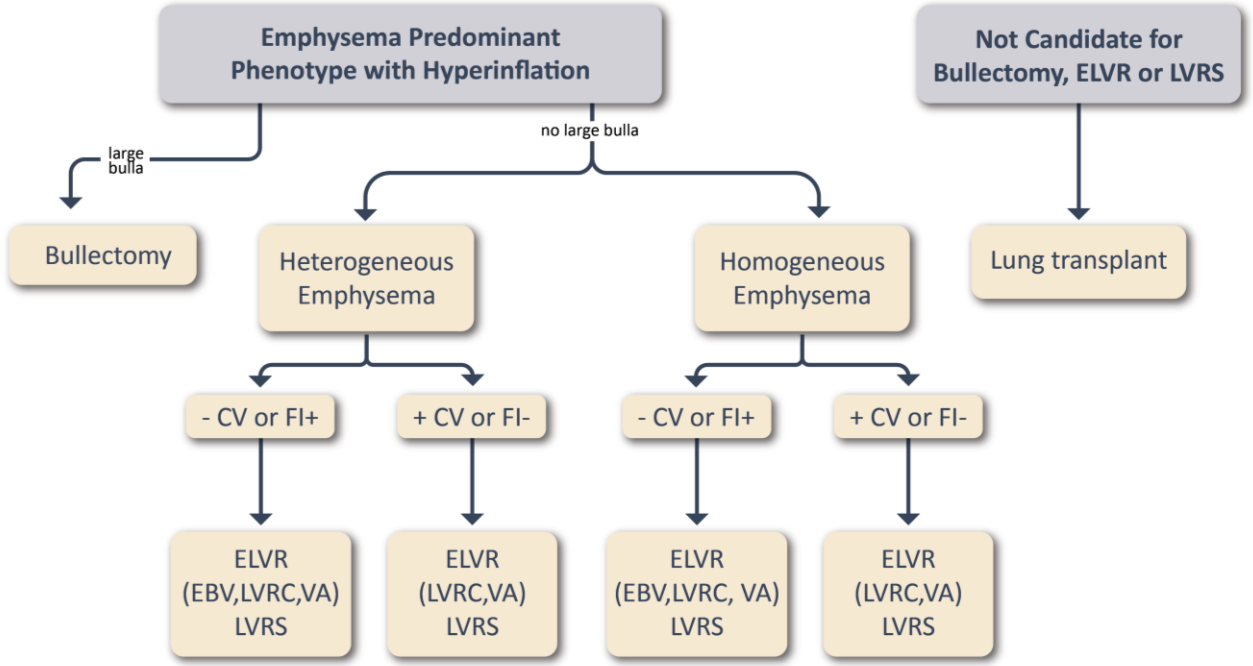
Surgical and Interventional Therapies in Advanced Emphysema

Figure 4.6



Note: not all therapies are clinically available in all countries. Long term ELVR outcomes or direct comparisons to LVRS are unknown.

Definition of abbreviations: CV, collateral ventilation measure by Chartis; FI + fissure integrity > 90% by HRCT; FI-, fissure integrity < 90% by HRCT; ELVR, Endoscopic Lung Volume Reduction, EBV, Endobronchial Valve; VA, Vapor Ablation; LVRC, Lung Volume Reduction Coil; LVRS, Lung Volume Reduction Surgery. Modified from Vogelmeier, AJRCCM, 2017

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KEY POINTS FOR THE USE OF NON-PHARMACOLOGICAL TREATMENTS

EDUCATION, SELF-MANAGEMENT AND PULMONARY REHABILITATION

- Education is needed to change patient's knowledge but there is no evidence that used alone it will change patient behavior .
- Education self-management with the support of a case manager with or without the use of a written action plan is recommended for the prevention of exacerbation complications such as hospital admissions **(Evidence B)**.
- Rehabilitation is indicated in all patients with relevant symptoms and/or a high risk for exacerbation **(Evidence A)**.
- Physical activity is a strong predictor of mortality **(Evidence A)**. Patients should be encouraged to increase the level of physical activity although we still don't know how to best insure the likelihood of success.

VACCINATION

- Influenza vaccination is recommended for all patients with COPD **(Evidence A)**.
- Pneumococcal vaccination: the PCV13 and PPSV23 are recommended for all patients> 65 years of age, and in younger patients with significant comorbid conditions including chronic heart or lung disease **(Evidence B)**.
- Covid-19 vaccination in line with national recommendations **(Evidence B)**.
- Tdap (dTaP/dTPa) vaccination for adults with COPD who were not vaccinated in adolescence to protect against pertussis (whooping cough) **(Evidence B)**.

NUTRITION

- Nutritional supplementation should be considered in malnourished patients with COPD **(Evidence B)**.

END OF LIFE AND PALLIATIVE CARE

- All clinicians managing patients with COPD should be aware of the effectiveness of palliative approaches to symptom control and use these in their practice **(Evidence D)**.
- End of life care should include discussions with patients and their families about their views on resuscitation, advance directives and place of death preferences **(Evidence D)**.

TREATMENT OF HYPOXEMIA

- In patients with severe resting hypoxemia long-term oxygen therapy is indicated **(Evidence A)**.
- In patients with stable COPD and resting or exercise-induced moderate desaturation, long term oxygen treatment should not be routinely prescribed. However, individual patient factors may be considered when evaluating the patient's needs for supplemental oxygen **(Evidence A)**.
- Resting oxygenation at sea level does not exclude the development of severe hypoxemia when travelling by air **(Evidence C)**.

TREATMENT OF HYPERCAPNIA

- In patients with severe chronic hypercapnia and a history of hospitalization for acute respiratory failure, long term noninvasive ventilation may be considered **(Evidence B)**.

INTERVENTION BRONCHOSCOPY AND SURGERY

- Lung volume reduction surgery should be considered in selected patients with upper-lobe emphysema **(Evidence A)**.
- In selected patients with a large bulla surgical bullectomy may be considered **(Evidence C)**.
- In select patients with advanced emphysema, bronchoscopic interventions reduce end-expiratory lung volume and improve exercise tolerance, quality of life and lung function at 6-12 months following treatment. Endobronchial valves **(Evidence A)**; Lung coils **(Evidence B)**; Vapor ablation **(Evidence B)**.
- In patients with very severe COPD (progressive disease, BODE score of 7 to 10, and not candidate for lung volume reduction) lung transplantation may be considered for referral with at least one of the following: (1) history of hospitalization for exacerbation associated with acute hypercapnia (Pco_2 >50 mm Hg); (2) pulmonary hypertension and/or cor pulmonale, despite oxyqen therapy; or (3) FEV_1 < 20% and either DLCO < 20% or homogenous distribution of emphysema **(Evidence C)**.

TABLE 4.10

Key Points for the Use of Non-Pharmacological Treatments

Table 4.11

Education, Self-Management and Pulmonary Rehabilitation	• Education is needed to change patient's knowledge but there is no evidence that used alone it will change patient behavior • Education self-management with the support of a case manager with or without the use of a written action plan is recommended for the prevention of exacerbation complications such as hospital admissions **(Evidence B)** • Rehabilitation is indicated in all patients with relevant symptoms and/or a high risk for exacerbation **(Evidence A)** • Physical activity is a strong predictor of mortality **(Evidence A)**. People with COPD should be encouraged to increase the level of physical activity although we still don't know how to best insure the likelihood of success
Vaccination	• Influenza vaccination is recommended in people with COPD **(Evidence B)** • The WHO and CDC recommends SARS-CoV-2 (COVID-19) vaccination for people with COPD **(Evidence B)** • The CDC recommends one dose of 20-valent pneumococcal conjugate vaccine (PCV20); or one dose of 15-valent pneumococcal conjugate vaccine (PCV15) followed by 23-valent pneumococcal polysaccharide vaccine (PPSV23) in people with COPD **(Evidence B)** • Pneumococcal vaccine has been shown to reduce the incidence of community-acquired pneumonia and exacerbations in people with COPD **(Evidence B)** • The CDC recommends Tdap (dTaP/dTPa) vaccination to protect against pertussis (whooping cough) for people with COPD that were not vaccinated in adolescence **(Evidence B)**, and Zoster vaccines to protect against shingles for people with COPD over 50 years **(Evidence B)**
Nutrition	• Nutritional supplementation should be considered in malnourished patients with COPD **(Evidence B)**
End of Life and Palliative Care	• All clinicians managing patients with COPD should be aware of the effectiveness of palliative approaches to symptom control and use these in their practice **(Evidence D)** • End of life care should include discussions with patients and their families about their views on resuscitation, advance directives and place of death preferences **(Evidence D)**
Treatment of Hypoxemia	• In patients with severe resting hypoxemia long-term oxygen therapy is indicated **(Evidence A)** • In patients with stable COPD and resting or exercise-induced moderate desaturation, long term oxygen treatment should not be routinely prescribed. However, individual patient factors may be considered when evaluating the patient's needs for supplemental oxygen **(Evidence A)** • Resting oxygenation at sea level does not exclude the development of severe hypoxemia when travelling by air **(Evidence C)**
Treatment of Hypercapnia	• In patients with severe chronic hypercapnia and a history of hospitalization for acute respiratory failure, long term noninvasive ventilation may be considered **(Evidence B)**
Intervention Bronchoscopy and Surgery	• Lung volume reduction surgery should be considered in selected patients with upper-lobe emphysema **(Evidence A)** • In selected patients with a large bulla surgical bullectomy may be considered **(Evidence C)** • In select patients with advanced emphysema, bronchoscopic interventions reduce end-expiratory lung volume and improve exercise tolerance, quality of life and lung function at 6-12 months following treatment. Endobronchial valves **(Evidence A)**; Lung coils **(Evidence B)**; Vapor ablation **(Evidence B)** • In patients with very severe COPD (progressive disease, BODE score of 7 to 10, and not candidate for lung volume reduction) lung transplantation may be considered for referral with at least one of the following: (1) history of hospitalization for exacerbation associated with acute hypercapnia (Pco_2 > 50 mmHg); (2) pulmonary hypertension and/or cor pulmonale, despite oxygen therapy; or (3) FEV1 < 20% and either DLco < 20% or homogenous distribution of emphysema **(Evidence C)**

CHAPTER 5: MANAGEMENT OF EXACERBATIONS

xvi. Chapter 5 on the topic of Management of Exacerbations has been expanded to include details of possible alternative causes of symptoms and **a new table on Diagnosis and Assessment** (Page 136)

ix. **A new definition of COPD Exacerbation** and a new set of parameters to assess exacerbation severity at the point of care has been included (Page 134)

DIFFERENTIAL DIAGNOSIS OF COPD EXACERBATION

WHEN THERE IS CLINICAL SUSPICION OF THE FOLLOWING ACUTE CONDITIONS, CONSIDER THE FOLLOWING INVESTIGATIONS:

PNEUMONIA
- Chest radiograph
- Assessment of C-reactive protein (CRP) and/or procalcitonin

PNEUMOTHORAX
- Chest radiograph or ultrasound

PLEURAL EFFUSION
- Chest radiograph or ultrasound

PULMONARY EMBOLISM
- D-dimer and/or Doppler sonogram of lower extremities
- Chest tomography – pulmonary embolism protocol

PULMONARY EDEMA DUE TO CARDIAC RELATED CONDITIONS
- Electrocardiogram and cardiac ultrasound
- Cardiac enzymes

CARDIAC ARRHYTHMIAS – ATRIAL FIBRILLATION/FLUTTER
- Electrocardiogram

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Confounders or Contributors to be Considered in Patients Presenting with Suspected COPD Exacerbation

Table 5.1

Most frequent	**Pneumonia**	• Chest radiograph
	Pulmonary embolism	• Clinical probability assessment (Hemoptysis, surgery, fracture, history of cancer, DVT) • D-dimer • CT angiography for pulmonary embolism
	Heart failure	• Chest radiograph • NT Pro-Brain Natriuretic Peptide (Pro-BNP) and BNP • Echocardiography
Less frequent	**Pneumothorax, pleural effusion**	• Chest radiograph • Thoracic ultrasound
	Myocardial infarction and/or cardic arrhythmias (atrial fibrillation/flutter)	• Electrocardiography • Troponin

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Diagnosis and Assessment

Table 5.2

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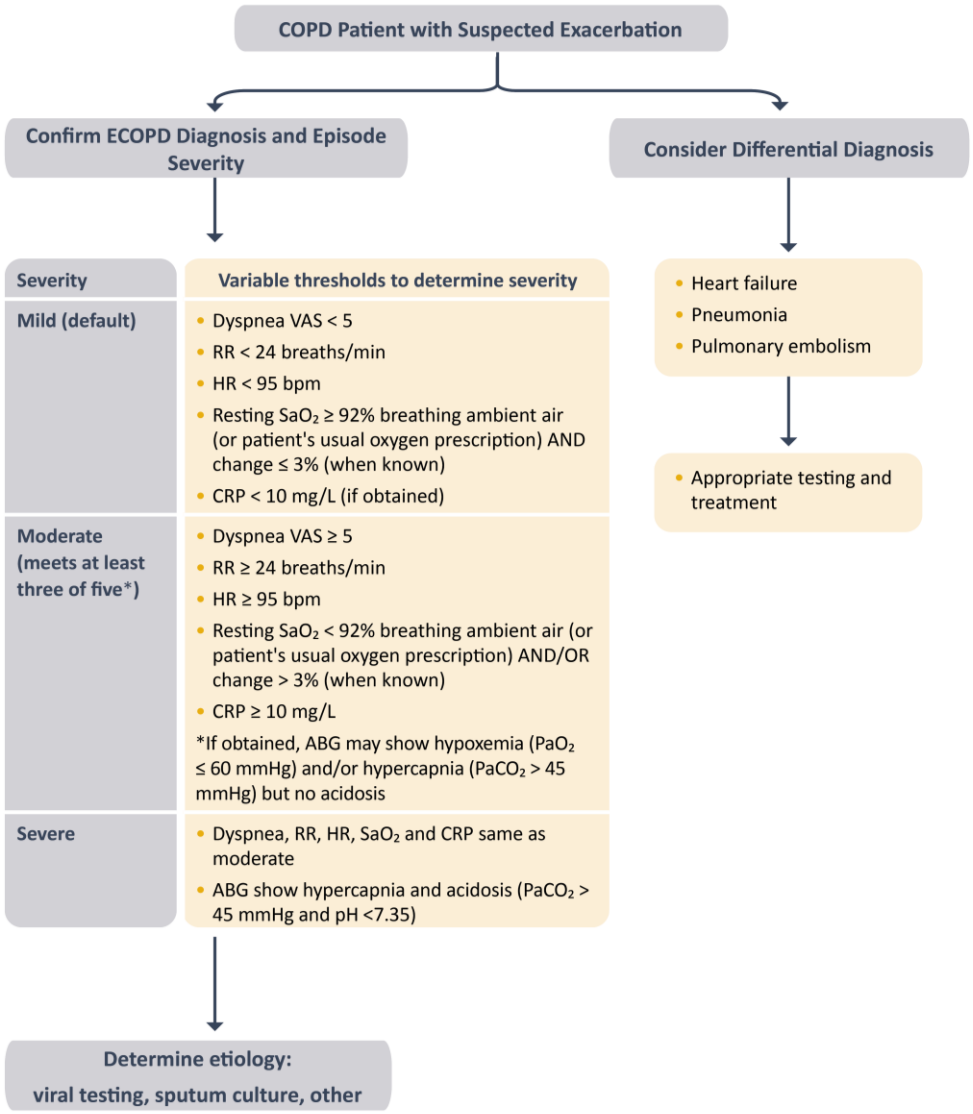
1.	Complete a thorough clinical assessment for evidence of COPD and potential respiratory and nonrespiratory concomitant diseases, including consideration of alternative causes for the patient's symptoms and signs: primarily pneumonia, heart failure, and pulmonary embolism.
2.	**Assess:** a. Symptoms, severity of dyspnea that can be determined by using a VAS, and documentation of the presence of cough. b. Signs (tachypnea, tachycardia), sputum volume and color, and respiratory distress (accessory muscle use).
3.	Evaluate severity by using appropriate additional investigations such as pulse oximetry, laboratory assessment, CRP, arterial blood gases.
4.	Establish the cause of the event (viral, bacterial, environmental, other).

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; VAS = visual analog scale.

Classification of the Severity of COPD Exacerbations

Figure 5.1



Adapted from: The ROME Proposal, Celli et al. (2021) Am J Respir Crit Care Med. 204(11): 1251-8. Abbreviations: VAS visual analog dyspnea scale; RR respiratory rate; HR heart rate; SaO_2 oxygen saturation; CRP C-reactive protein; ABG arterial blood gases; PaO_2 Arterial pressure of oxygen.

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Summary

- New definition of AECOPD
  - **The Rome Proposal vs. the Lancet Commission**
- New definition of COPD
  - Persistent airflow limitation → **progressive airflow limitation**
  - "caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development" → "**a heterogeneous lung condition**"
- Proposed taxonomy (**etiotypes**) for COPD
- Updated treatment
  - Group A,B,C, and D → **Group A,B, and E**
  - **LABA+LAMA ↑ and LABA+ICS ↓**