Thursday, October 14, 2021
State of the Art
AJRCCM

TREATMENT TRIALS IN PRE-COPD AND YOUNG COPD: TIME TO MOVE FORWARD

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

*Joint first authors; +joint last authors

1. Weill Cornell Medicine, NYPPresbyterian Hospital, New York, NY, USA.
2. Catedra Salut Respiratoria, University of Barcelona; Institut Respiratori, Hospital Clinic, Barcelona; IDIBAPS, Barcelona; CIBERES, Spain
3. Brigham and Women's Hospital. Harvard Medical School, Boston, MA, USA
4. University of Michigan Health System, Ann Arbor, MI, USA.
5. National Heart and Lung Institute, Imperial College, London, UK.
6. University of Alabama at Birmingham, Birmingham, AL, USA
7. Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, UK
8. Lee Kong Chain School of Medicine, Nanyan Technological University, Singapore.
9. Savara, Inc., Washington, DC.
10. AstraZeneca, Gaithersburg, MD, USA
11. Clinical Development, Research and Early Development, Respiratory & Immunology, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden
12. Centro de Investigacion Biomedica en Red de Enfermedades Respiratorias, Barcelona, Spain.
13. Royal Devon and Exeter Hospital, Exeter, UK.
14. St. George's University of London, London, UK
15. University of Illinois, Chicago, IL, USA.
16. Nimigra, LLC, Durham, NC
17. University of Arizona, Tucson, AZ, USA.
18. AstraZeneca, Cambridge, UK
19. Observational and Pragmatic Research Institute, Singapore and University of Aberdeen, Scotland.
20. LungenClinic Grosshansdorf and Dept of Medicine, Christian Albrechts University Kiel, Members of the German Center for Lung Research (DZL), Grosshansdorf, Germany
21. DevPro Biopharma, Basking Ridge, NJ, USA.
22. Division of Infection, Immunity and Respiratory Medicine, University of Manchester, and Manchester University NHS Foundation Trust, Manchester, UK.

23. Department of Medicine, Pulmonary and Critical Care Medicine, University of Marburg, Member of the German Center for Lung Research (DZL), Marburg, Germany
24. Johns Hopkins Medicine, Baltimore, MD, USA.
25. COPD Foundation, Washington, DC, USA

Corresponding author:
Fernando J. Martinez, MD, MS
1305 York Avenue, Box 96, Room Y-1059
New York, NY 10021
Telephone: 646.962.2748
Fax: 646.962.0286
E-mail: fjm2003@med.cornell.edu.

Abstract word count: 250
Text body word count: 5341; 172 References; 5 Tables; 2 Figures
Supplementary Material: 1 Table, 1 Figure

Author's contributions

FJM, AA, BRC, RTS, JAW prepared first version of manuscript and finalized last version. FJM, AA, BRC, MKH, JA, SPB, PC, SHC, BC, PD, CADS, GD, PD, MD, RF, DMH, PJ, JAK, NL, FDM, HM, DP, KFR, CR DS, JV, CFV, RAW, and RTS wrote versions of key sections, reviewed, and approved the final version.

Keywords:

COPD, Early, young age, pre-COPD, Clinical Trials

ABSTRACT

Chronic Obstructive Pulmonary Disease is the end-result of a series of dynamic and cumulative gene-environment interactions over a lifetime. The evolving understanding of COPD biology provides novel opportunities for prevention, early diagnosis, and intervention. To advance these concepts we propose therapeutic trials in two major groups of subjects: those "young" individuals with COPD and those with pre-COPD. Given that lungs grow to about 20 years of age and begin to age at approximately 50 years, we consider "young" COPD those patients in the age range of 20-50 years. Pre-COPD relates to individuals of any age who have respiratory symptoms with or without structural and/or functional abnormalities, in the absence of airflow limitation, and who may develop persistent airflow limitation over time. We exclude from the current discussion infants and adolescents because of their unique physiological context and COPD in older adults given their representation in prior randomized clinical trials (RCTs). We highlight the need of RCTs focused on young COPD or Pre-COPD patients to reduce disease progression, providing innovative approaches to identifying and engaging potential study subjects. We detail approaches to RCTs design including potential outcomes such as lung function, patient reported outcomes, exacerbations, lung imaging, mortality, and composite endpoints. We critically review study design components such as statistical powering and analysis, duration of study treatment, and formats to trial structure including platform, basket, and umbrella trials. We provide a call to action for treatment RCTs in (1) young adults with COPD and (2) those with pre-COPD at any age.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a major global public health problem. Conventionally believed to be a self-inflicted disease due to tobacco smoking that affects the elderly (1), recent research has shown that COPD is the end-result of a series of dynamic and cumulative gene-environment interactions over the lifetime, that go beyond smoking (2), can begin early in life (in-utero, infancy and/or adolescence) (3-6), and result in varying lung function trajectories (trajectome), several of which lead to COPD in adulthood (7-9) (**Figure 1**). This new understanding of COPD provides novel opportunities for prevention, early diagnosis, and intervention (10). This state-of-the-art review seeks to **launch a call to action to investigators, funding agencies, industry, and regulators to initiate treatment trials in (1) young adults with COPD and (2) those with pre-COPD, this is those with respiratory symptoms, abnormal imaging and/or lung function without evidence of airflow limitation who may (or may not) develop COPD with time (11, 12).**

NOSOLOGY

A first, key step to this end is to avoid nosological confusion. Accordingly, we propose to adopt the following terminology (Table 1).

COPD

As defined by GOLD, COPD is a disease "*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*"(13).

Early COPD

According to the Merriam-Webster dictionary, "early" means "near the beginning of a process." Because COPD can start early in life (3-5), and generally takes a long time to manifest clinically

(8), defining whether someone suffers "early" COPD is difficult (14). Some studies have used "*mild*" airflow limitation as a surrogate for "*early*" disease (15). This assumption would be correct if all patients started their journey from a normal peak lung function in early adulthood and COPD would have progressed similarly in all of them. Alas, this assumption is incorrect (**Figure 1**) (8). "Mild" (like moderate or severe) airflow limitation can occur at any age (**Figure 1**) and only describes the "severity" of airflow limitation. Therefore, we propose that "mild" should not be used to identify "early" COPD. Likewise, we recognize that mild airflow limitation may not always be COPD, at least according to the current definition of airway diseases. Finally, 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 (16). Accordingly, we propose to use the term "early COPD" only to discuss "biological early."

COPD in young subjects

The term "young" directly relates to the age of the subject and may seem straightforward and confusion less. However, to some extent, "young" is also a value judgment that depends on the age of the observer and the part of the globe where the individual lives, as life expectancy varies greatly in different parts of the world. For the discussion that follows, given that lung growth and development reach its peak at around 20-25 years of age and begin to decline at 45-50 years (17), we propose to operationally consider "young" patients with COPD as those included in an *age range of 20-50 years* (**Figure 1**). In population-based studies these younger individuals have a higher prevalence of prior asthma diagnosis (18). It is anticipated that in young patients with COPD preventive measures and pharmacological interventions may result in better outcomes than in older patients (10, 19, 20) and may slow down disease progression (10). Importantly, this age range can include patients who never achieved normal peak lung function in early adulthood and/or those with early accelerated lung function decline (**Figure 1**) which may have different underlying mechanisms (i.e., endotypes (21)) and may therefore require different therapeutic interventions (5, 22, 23).

Pre-COPD

The term pre-COPD has been recently proposed to identify individuals of *any age* who have respiratory symptoms with/without structural and/or functional abnormalities, in the absence of airflow limitation ($FEV_1/FVC \geq 0.7$), and who may (or may not) develop persistent airflow limitation (i.e., COPD) over time (11, 12). This term includes a heterogeneous population of patients. So far, several subtypes of pre-COPD have been reported. The best studied one includes patients with non-obstructive chronic bronchitis (**NOCB**), in whom symptoms are associated with significant morbidity regardless of whether they ultimately progress to airflow limitation (11). Other, less well studied, subtypes of pre-COPD are subjects without airflow limitation who have emphysema detected with computed tomography (**CT**) (24), individuals with Preserved Ratio Impaired Spirometry (**PRISm** – post-bronchodilator $FEV_1 < 80\%$ predicted and $FEV_1/FVC \geq 0.70$) (25), and subjects with low diffusing capacity for carbon monoxide (DLCO) (26) or rapid FEV_1 decline (27). The natural history and potential response to treatment these heterogenous conditions is unknown.

Disease activity vs. disease progression

These two terms are related but not synonymous. Disease "*activity*" relates to the level of activation of the pathobiological processes that cause the disease (14), whereas disease "*progression"* refers to a deterioration over time in an objective marker of pathology, such as by computed tomography, or function. The relationship between disease "activity" and disease "progression" in COPD remains unclear. Disease activity is probably a necessary but insufficient condition for disease progression. For instance, a given patient may suffer frequent exacerbations (a clinical surrogate marker of an "active" disease") without a clear deterioration in lung function (a marker of disease "progression"). We currently lack validated biomarkers to identify whether or not specific endotypes are "active" in COPD (28) and, as a result, disease "activity" in COPD is often estimated *post-hoc* by evidence of disease "progression" (29). Of note, however, in older patients with moderate-severe COPD, persistent systemic inflammation has been associated with increased all-cause mortality and exacerbation frequency (30), and the use of inflammometry and multi-dimensional assessment to guide treatment improved several patient related outcomes (**PROs**) at three months in a small pilot randomized controlled trials (**RCT**) (31). Whether these limited preliminary data apply to younger patients is unknown. Likewise, patients with milder

airflow limitation appear to progress (in terms of FEV_1 decline) faster than those with more severe airflow limitation (32) so identifying biomarkers of disease activity associated with different lung function trajectories (**Figure 1**) would be of great value (33, 34). In any case, future treatment trials in young patients should ideally target individuals at risk of disease progression based on validated biomarkers of disease activity.

Primary, secondary, and tertiary prevention

Primary prevention aims at preventing a disease before it occurs by eliminating exposures to risk factors and/or increasing resistance to it should exposure occur. Primary prevention of COPD is key in children and adolescents (**Figure 1**) but likely relates more to public health measures than to therapeutic interventions, although we acknowledge that boosting "catch-up" of impaired lung function in early life may deserve specific investigation (8, 24, 35, 36). Secondary prevention aims to reduce progression once disease has already manifested. This is, precisely, the goal of this call for action for treatment trials in young patients. Finally, tertiary prevention aims at reducing the impact of an ongoing illness, has been more frequently considered in the setting of COPD in older patients, and has been extensively investigated in previous RCTs.

TREATMENT TRIALS IN YOUNG COPD AND PRE-COPD PATIENTS

The discussion that follows focuses on treatment trials in young (20-50 years of age) adults with COPD or Pre-COPD (any age). These trials are needed as young patients with COPD or pre-COPD may already suffer a significant burden of disease (37, 38). In these patients, treatment cannot be neglected, although the scientific evidence supporting the best therapeutic alternatives has not been generated. In addition, it is likely that a therapeutic intervention in younger individuals with the drugs currently available, before advanced tissue destruction, multimorbidity and effects of ageing become clinically relevant, may be more effective (10) and may reduce/arrest disease progression. Finally, the combination of primary and secondary preventive measures aimed at avoiding all those factors associated with low lung function in different age bins with appropriate, evidence-based, treatment of younger COPD patients, has the potential to

reduce the societal burden of disease, promote respiratory health and, eventually the development of COPD (39).

Although the results of large multicenter RCTs have driven our current understanding and management of COPD, they have historically faced a number of limitations (**Table 2**) (40-43). These and other considerations may apply also to future treatment trials in young patients and are discussed below.

Case Finding/Recruitment

In a recent, large epidemiological study in China, the prevalence of COPD in adults aged 20-49 years was 16.4% in males and 7.4% in females (**Figure 2**) (44), so finding and recruiting these patients into an RCT may require a combined strategy. Although widespread population spirometric screening has not been traditionally advocated (45), targeted case finding approaches are promising (46). Indeed, there has been a recent proposal supporting the use of forced spirometry in the general population (even in children and adolescents) as a marker of not only respiratory diseases but global health (47). Symptom-based instruments (e.g., COPD-PS (48), IPAG (49), COPD-Q (50), and LFQ (51)) and PROs questionnaires (e.g., CAT (52), CAPTURE (53, 54) or CAT/CAAT (55)) were have been developed or adapted for case finding in patients with established COPD. Their utility in young patients is unclear as most were developed and tested in those over 40 years of age. Mucus hypersecretion can be better identified using the symptoms component of the SGRQ or the phlegm question in the CAT rather than the Medical Research Council (**MRC**) definition for chronic bronchitis (CB) (11, 56-59). Reduced physical activity measured by daily accelerometer recordings is reduced in COPD patients detected by spirometry screening (60), so PROs measuring physical activity (e.g. Clinical visit-PROactive Physical Activity in COPD (C-PPAC) (61)) could potentially be used to identify these patients. Primary care networks may be particularly crucial in identifying potential young patients from electronic medical records (62), either by identifying patterns of risk factors, biomarkers, or in identifying symptoms before COPD is diagnosed (63). Finally, public advertising campaigns via traditional print or electronic media, social media campaigns and collaboration with non-profit advocacy organizations can be useful aids to boost patient recruitment. The power of the patient-

led collaborative "Venture Philanthropy" effort by the Cystic Fibrosis Foundation (64) transformed Cystic Fibrosis from a highly mortal disease in early life to a disease that can be treated with precision (65). The COPD Foundation has recently launched a multidisciplinary collaborative initiative, COPD360Net, with the mission to support the development and adoption of novel digital health tools, medical devices and therapeutics that treat COPD, prevent its progression, and improve lives of patients with COPD and related chronic lung conditions at all stages of disease (Supplemental **Figure 1**). COPD360Net is currently seeking partners to conduct a collaborative platform trial in young patients with Pre-COPD and NOCB.

Smoking exposure/status

Previous RCTs in COPD have studied (older) current or former smokers. As prior studies suggested that variation in smoking status impacted the range of lung function decline (66) and mortality (67), previous history and current active smoking should be carefully monitored and adjusted for in future therapeutic trials. This is particularly relevant as smoking cessation should be encouraged given its beneficial effects (66, 68) and is facilitated by numerous interventions (69). Notably, about a third of COPD patients around the world are never smokers (70) and many other environmental risk factors are associated with low lung function through life. For example, early studies of e-cigarette exposure has been suggested to result in altered pulmonary function and structure (71, 72). Similarly, occupational exposure and air pollution (73, 74) have been associated with respiratory disease and should be considered in study design, conduct and analyses . It is imperative to study young never smokers with COPD (5, 35, 75-79) exposed or not to other known (indoor pollution) or unknown environmental factors as well as those impacted by abnormal lung development before the age of 20.

Nonrespiratory medications

It is possible that nonrespiratory medications may influence the development of COPD or its complications. For example, it remains unclear if statin therapy can favorably influence noncardiovascular complications of COPD (80). Preclinical data with metformin have suggested improvement in the development of emphysema with cohort studies providing variable clinical

correlates (81, 82). It will be important during therapeutic trials to carefully record non-respiratory medications.

Outcome measures

The outcome measure of any trial should be reproducible over time, have known biological variability, be responsive to treatment, and be relevant to the targeted trait. In young patients, the following ones could be considered.

Lung function

FEV_1 is a simple, relatively inexpensive, reproducible measure recognized as an outcome measure by regulatory authorities, including the US Food and Drug Administration (**FDA**) and the European Medicines Agency (**EMA**). Further, FEV_1 decline has been traditionally used as a measure of disease progression in COPD (83). However, in young patients there are important additional considerations. First, in these patients a reduced FEV_1 value may result from abnormal lung development and/or early enhanced decline (**Figure 1)** (7) and, in the absence of historic data, these two trajectories are difficult to define (7). Second, absolute decline in FEV_1 is faster in patients with milder airflow limitation (32), who might be younger. If so, this may facilitate studying the impact of interventions on FEV_1 decline in younger patients. Absolute FEV_1 decline is also subject to bias from starting lung size which is influenced by factors such as height and gender. **Table 3** enumerates the change in FEV_1 among RCTs targeting mild to severe COPD patients with average ages 50-65. A systematic review of RCT suggests that a 5.0 ml/yr. reduction (95% CI 0.8-9.1 ml/yr.) has been suggested in the rate of FEV_1 decline in active treatment arms compared with placebo (84). Arguably, younger individuals show faster FEV_1 decline (32) because they have more lung function left to lose, and this might make it easier to study the impact of interventions on FEV_1 decline. However, a single FEV_1 measurement is not a good predictor of the future FEV_1 trajectory and rapid FEV_1 decliners can only be identified in retrospect (85, 86). Thus, it may be more pragmatic to enrich the study population using surrogate markers of accelerated FEV_1 decline (87), including chronic mucus hypersecretion (88), prior frequent exacerbations (32, 89), or imaging features as described below.

Longer trials extending beyond 3 years (the minimum currently required by Regulators) reduce FEV_1 decline variability and, accordingly, the sample size required. **Table 3** highlights that trials to evaluate rate of decline have generally been long in duration and that longer trials reduce variability. The common approach to conduct a three year trial still requires a relatively large sample. For example, if we assume a SD of 100 mL/yr. and wish to detect a difference of 12 mL/yr. approximately 1500/group are required to be 90% powered for α=0.05. If instead SD 80mL/yr. and effect size of 15 mL/yr. are assumed, then this requirement for 90% power drops to approximately 600/arm. The advantage of longer trials needs to be counterbalanced by the challenge of retaining sufficient subjects and avoiding issues with biases introduced by differential withdrawal. As such, it will be key to carefully and prospectively define the estimand (90) that we are trying to estimate with consideration to how subjects who prematurely discontinue the intervention and/or leave the trial will be handled. In any case, FEV_1 decline should be measured in studies of young patients to characterize the population and to evaluate potential disease modification. Other lung function measures, like novel spirometric parameters (91-93), inspiratory capacity, body plethysmography (to quantify hyperinflation), oscillometry, DLCO, may also deserve investigation in this population.

Symptoms/Health status/PROs

The CAT is likely to be the preferred option in most cases, irrespective of whether participants have been recruited on the basis of mucus hypersecretion, breathlessness or exercise limitation as its multi-dimensional nature will capture changes in each of these features. Unless study participants are symptomatic, symptom scores, PROs and health-related quality of life (**HRQL**) measures will not be able to detect improvement with interventions, as CAT score values <10 are not associated with a noticeable effect on daily life (94). Yet, available evidence shows that young patients are not asymptomatic (37) and that COPD patients with mild airflow obstruction (not necessarily young) do have marginally elevated SGRQ and CAT scores (57, 58, 95, 96), suggesting that there is potential for improvement. In fact, a trial in average age of 65 years-old COPD patients with mild-moderate airflow limitation showed an effect on CAT scores (15), and a subgroup analysis of the EMAX study (mean age 65 years) showed that magnitude of

symptomatic benefit of dual bronchodilator compared to monotherapy was similar in patients with CAT scores ~10 or ~20 (97). Measures of physical activity (e.g., Daily-PROactive Physical Activity in COPD (**D-PPAC**) (61) may also be considered. Bronchodilator trials in GOLD grade 1 patients showed variable results (98, 99). What constitutes a Minimal Clinically Important Difference (MCID) in patients with low level of symptoms (100, 101), and whether therapeutic interventions in these patients would have a large enough effect to be detected, is uncertain. In summary, the optimum symptom score, PRO or HRQL measure to use in a particular trial will depend on the inclusion criteria. Lastly, measures of health care utilization should also be considered as relevant endpoints given their impact on patients and the health care system (102, 103).

Exacerbations

Exacerbations of COPD (**ECOPD**) remain a central, valid, and important tenet for the adequate assessment of clinical disease and therapeutic needs, and for RCTs they represent an important outcome measure (18, 102, 104, 105). Their prevalence and severity in young patients are still not well defined but they do indeed occur (37). ECOPD in young individuals may be influenced by symptom reporting. This, in turn, may be subject to individual variability in perception (106) and, further prejudiced by societal and cultural norms for interpreting and reporting of respiratory symptoms, as well as by local primary care set-up and its interface with tertiary hospitals. We do not know if frequent ‘exacerbator’ phenotypes exist in young patients, so more epidemiological work on this group would assist in developing interventional studies.

Lung Imaging

Imaging biomarkers can be used both to identify individuals at high risk for disease progression as well as endpoints in treatment trials in young patients. In particular, CT metrics of small airway abnormality may be most helpful to enrich the study population with young patients at higher risk for disease progression. Density-based metrics have the strongest supportive data for reproducibility making them attractive as clinical endpoints, although they may be relevant only for specific therapeutic interventions.

Several *airway abnormalities* on chest CT scans correlate with dyspnea, quality of life and functional capacity, and predict lung function decline (**Supplemental Table 1)** (57, 107). Pi10, a measure of the thickness of medium size airways, relates to incident COPD over 3-5 years (108, 109) and is sensitive to change over time (110), even over short follow-up periods (111). Parametric response mapping (**PRM**) matches inspiratory and expiratory images to estimate non-emphysematous gas trapping or functional small airways disease (**PRM^{fSAD}**) and also predicts lung function decline (112, 113). The normal density E to I Ratio, another measure of gas trapping due to small airway disease, is also associated with FEV_1 decline (114). Total airway count correlates with the number of terminal bronchioles on micro-CT (115) and is associated with FEV_1 decline, especially in those with mild to moderate disease (116). Airway fractal dimension (**AFD**), a measure of the complexity of airway branching, is lower in patients with more severe airflow limitation and is also associated with FEV_1 decline (117). Finally, the airway surface area to volume ratio reflects a combination of airway loss and airway narrowing, is associated with FEV_1 decline, and can be used to phenotype individuals into those with predominant loss *vs.* narrowing of airways (118, 119).

Density-based measures of emphysema are also associated with lung function decline (120, 121) and mortality (117, 119, 122-125). CT emphysema progresses over time, particularly in current smokers (126, 127). The lung density metric is already in use in α-1 antitrypsin deficiency, a known cause of COPD in the young, as primary endpoint to assess the impact of interventions targeting attenuation of disease progression (128, 129). The correlation between emphysema and lung function is weaker compared to metrics of small airway abnormality (130, 131), but the reproducibility for PRM emphysema (**PRM^{Emph}**) is higher (132). This can allow a smaller sample size in RCTs (133). Finally, both PRM^{Emph} and PRM^{fSAD} have histologic validation with human lung tissue (134). Studies using CT measures of lung *biomechanics* suggest that once emphysema is initiated, mechano-transduction can accelerate further development of emphysema; hence CT indices that assess alterations in lung biomechanics have been associated with FEV_1 decline and BODE (125, 135). Qualitative assessment of mucus plugs on chest CT has been associated with ECOPD (136).

Other imaging techniques also hold promise. For instance, polarized gas MRI can identify abnormalities in diffusion and ventilation, which may precede the development of clinically overt disease (137) .

Mortality

Several issues need consideration in relation to mortality as a potential outcome in future studies of young patients. First, the comparison of death rates in major COPD trials in the 2000s (40, 43) and 2010s (138) shows that, fortunately, the risk of mortality in COPD is decreasing and may hopefully continue to decrease in the near future. Second, life expectancy varies widely across the world, so geographical variations will have to be considered in any future study in young patients. Finally, death rates are substantially lower in younger (20-50 years) than older COPD patients included in previous studies (40, 43, 138), and this may have a direct impact on sample size estimation. For instance, in the United States in 2017 the death rate in the 35-54 age group was about 300 per 100,000 persons (139). If we hypothesize that COPD may increase this risk two- or three-fold, estimated deaths in a population of young patients would be in the range of 600 to 900 deaths per 100,000 in a given year. Then, if a given therapeutic intervention was to reduce mortality in these patients by 30% (likely an optimistic estimation), an RCT with mortality as a primary endpoint would require recruiting about 80,000 patients, significantly more than those recruited in TORCH, UPLIFT and SUMMIT, which randomized from 6,000 to 16,000 patients (40, 43, 138). These considerations make mortality an unlikely useful outcome measure in future treatment trials in young patients.

Composite endpoints

A composite endpoint combines different individual endpoints to increase the frequency of events, allowing RCTs to be conducted with fewer participants and/or to be shorter. A composite endpoint also enables different aspects of a disease to be evaluated together, potentially providing a broader view of the impact of a therapeutic intervention and can be used to reduce bias caused by subjects who prematurely discontinue. The components of a composite endpoint need to be carefully selected to be sufficiently independent and of similar clinical relevance. The

frequency of each component should ideally be similar, so that more frequently occurring component(s) do not dominate. Alternatively, each component can be weighted differently. For instance, in COPD trials in older patients with severe COPD, although ECOPD is likely more frequent than death both could be components of a potential composite endpoint. In contrast, the lesser anticipated mortality of young patients suggests that such a composite endpoint may be even more dominated by ECOPD, even if these events are less prevalent than in older COPD patients. *Post-hoc* analysis of data from the UPLIFT trial of 5,992 patients with COPD randomized to receive tiotropium *vs.* usual care, studied over 4 years showed that a composite index consisting of death, respiratory failure, hospitalized exacerbations, and trial dropout due to COPD worsening could reduce the number of patients needed to achieve a significant outcome by half (140).

The clinically important deterioration (**CID**) composite endpoint, which combines worsening of PROs and FEV_1 with ECOPD, was designed for short COPD clinical trials (141) and several studies showed significant treatment differences (142-144). Further, longer studies demonstrated that CID events during the first 6 months of the study predict later mortality (145-147), suggesting that pharmacological interventions that modify CID frequency in short term trials may have longer term benefits. The use of CID in studies in young patients needs to consider several aspects. It is unclear if the MCID threshold values determined in older patients (4-unit worsening for SGRQ and 100 ml decrease for FEV_1) are valid in younger patients (141). Likewise, the frequency and variability of CID components varies between cohorts with different characteristics, so they need to be established in a cohort of young patients, as they dictate the sample size calculations of future studies. In summary, CID provides a framework for a potential composite endpoint in young patients, but methodology work is needed to identify the most appropriate components and define appropriate MCID thresholds. Other potential composite endpoints to consider in this population include the Early Clinically Important Improvement (ECII) (148) and COPDCompEx (see above) (149). An alternative to using a composite endpoint would be to jointly model the relevant endpoints that indicate deterioration (150), an approach that has been utilized in oncology trials (151).

Treatable traits, endotypes and biomarkers

As COPD is complex and heterogeneous, its clinical management requires a personalized approach. To this end, a management strategy based on treatable traits (**TTs**) has been proposed (152). TTs can be recognized based on their clinical characteristics (i.e., phenotypes) and/or through validated biomarkers of specific pathobiological mechanisms (i.e., endotypes) in the pulmonary, extra-pulmonary, and behavioral/environmental domains (152). TTs can coexist, interact, and change with time (spontaneously, or as a result of treatment) in the same patient (152). Because management guided by TTs can improve clinical outcomes (31), the design of future treatment trials in young patients needs to consider their presence or absence. Likewise, it should be noted that endotypes may vary with age, so they may differ in young and older COPD patients and improved understanding derived from ongoing research in young individuals may inform future treatment guidelines.

A promising biological marker is circulating eosinophils. RCTs in moderate to very severe COPD patients have shown that higher blood eosinophil counts at baseline are associated with greater benefits from inhaled corticosteroids (**ICS**) (153). This biomarker is now used in clinical practice to guide ICS use in patients with a history of exacerbations (154). Bronchoscopy and sputum studies in COPD patients have demonstrated that higher blood eosinophil counts are associated with increased lung eosinophil numbers and a profile of T2 inflammation, providing an explanation for the differential ICS effect (155, 156). Furthermore, lower blood and sputum eosinophils are associated with greater presence of proteobacteria (157, 158), with increased bacterial infections and pneumonia observed in these individuals (159). Clinical trials in younger COPD patients may be able to utilize blood eosinophil counts to select subgroups with distinct inflammation and microbiome profiles, and there may be considerable potential for ICS or other interventions targeting T2 inflammation in younger COPD patients with higher eosinophil counts. It is hoped that with improved understanding of the biological underpinnings behind COPD in young individuals or those with pre-COPD therapeutic approaches to be tested will be targeted to specific TTs.

Type of intervention

Pharmacological interventions are likely to be central in treatment trials of young adults with COPD, but other types of intervention may also be considered, alone or in combination with drug interventions. For instance, smoking cessation measures will have to be incorporated in any study design, even to get the approval of IRBs. Likewise, promotion of healthy lifestyle (exercise, diet, sleep, inhalational substance avoidance) will have to be considered as well.

Placebo or comparator

Approved treatments for COPD do not have a lower age limit but the scientific evidence supporting them has been generated in older populations. Thus, young patients are often treated without evidence for their effectiveness in COPD. As there are no specific approved treatments for COPD in young patients there is no age specific standard of care comparator. On the other hand, many currently available treatments are used in younger asthmatics, and the use of a placebo may prove challenging depending on the agent being tested.

Statistical power

Due to the relative lack of data on outcome measures in young patients, statistical power calculations will rely on information from observational cohorts (such as Early COPD in UK, ECLIPSE, COPDGene or SOURCE in the US, CADSET in Europe (160) and TRAIT in Japan (161)) and consortia that include a proportion of young patients (**Table 5**), electronic medical records, and/or blinded sample size reassessment/adaptive approaches and better define clinical trials duration. Likewise, the expected treatment effect sizes are not well established, although the expectation is that treatment differences might be greater in younger patients with (presumably) milder airflow limitation.

Platform trials

There is increasing interest in developing innovative approaches to enhance efficiency of clinical trials while testing numerous questions at the same time; master protocols such as umbrella (multiple targeted therapies in the context of a single disease), basket (study a single targeted

therapy in the context of multiple diseases or disease subtypes), and platform (multiple targeted therapies in the context of a single disease in a perpetual manner) trials are such an approach (162). Given potentially heterogeneity in patient populations platform trials may reflect a potential alternative to consider as they can invoke adaptive designs where progress is periodically re-assessed, and participants are reallocated from ineffective treatments to contribute to the overall outcome (163). Master protocol approaches, including platform trials, have been principally used in oncology (64) but have seen a tremendous increase in the setting of the COVID-19 pandemic (164). An initial exploratory study in young patients could be done using a master protocol design, which offers the advantage of evaluating multiple therapies (162). This approach would benefit from collaborations among multiple stakeholders, successfully used in the COVID-19 era (165), including industry partners and regulatory agencies.

Maintaining participant commitment in long clinical trials

Younger patients with COPD may be less motivated to participate in RCTs, as they are likely to be employed, caring for a young family, unlikely to be symptom-limited and more likely to relocate. Hence, developing a strong relationship with participants will be key as will be conducting trials through mechanisms that have broad geographic reaches. Although the primary outcome assessments are likely to be clinic-based, the use of digital health technology for interim assessments, monitoring trial medication adherence, and digital trial communication may aid. Regular participants contact to review symptoms, provide updates on trial progress, and appropriate subject compensation will be important to reduce dropouts during follow up. Many outcomes can be followed using appropriately anonymized electronic medical records that enhance the quality of the data and assess an intervention's cost-effectiveness.

Future Steps

It is clear that earlier intervention in younger patients with COPD or those at risk with pre-COPD will be a crucial next paradigm in the management of this impactful disorder. The most critical next steps now involve the design and development of specific RCTs in individuals with young

COPD and pre-COPD. **Table 5** enumerates potential issues and approaches to consider in their design.

CONCLUSIONS

Designing treatment trials in young patients and pre-COPD patients is complex. However, the barriers mentioned herein can be overcome, and the potential rewards in terms of knowledge and improved health by conducting successful trials are likely substantial. Now is the time to refine an approach to a collaborative initiative to modify the course of the 3rd leading cause of death in the world and a significant cause of morbidity globally. This requires commitment from Industry and Government funders and partnerships among diverse international stakeholders to implement platform trials utilizing harmonized methodology and standard outcome measures that will generate robust data. These can be integrated to develop evidence-based personalized preventive and therapeutic interventions that modify disease progression based on risk factors and/or treatable traits (152). Working together and acting earlier in young patients and patients with pre-COPD (10) can reduce the global burden of COPD (39).

REFERENCES

1. Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med J* 1977; 1: 1645-1648.
2. Breyer-Kohansal R, Faner R, Breyer MK, Ofenheimer A, Schrott A, Studnicka M, Wouters EFM, Burghuber OC, Hartl S, Agusti A. Factors Associated with Low Lung Function in Different Age Bins in the General Population. *Am J Respir Crit Care Med* 2020; 202: 292-296.
3. Martinez FD. The origins of asthma and chronic obstructive pulmonary disease in early life. *Proc Am Thorac Soc* 2009; 6: 272-277.
4. Martinez FD. Early-Life Origins of Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2016; 375: 871-878.
5. Agusti A, Faner R. How to Define Early Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2018; 198: 973.
6. Celli BR, Wedzicha JA. Update on Clinical Aspects of Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2019; 381: 1257-1266.
7. Lange P, Celli B, Agusti A, Boje Jensen G, Divo M, Faner R, Guerra S, Marott JL, Martinez FD, Martinez-Camblor P, Meek P, Owen CA, Petersen H, Pinto-Plata V, Schnohr P, Sood A, Soriano JB, Tesfaigzi Y, Vestbo J. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2015; 373: 111-122.
8. Agusti A, Faner R. Lung function trajectories in health and disease. *Lancet Respir Med* 2019; 7: 358-364.
9. Ramirez-Venegas A, Sansores RH, Quintana-Carrillo RH, Velazquez-Uncal M, Hernandez-Zenteno RJ, Sanchez-Romero C, Velazquez-Montero A, Flores-Trujillo F. FEV1 decline in patients with chronic obstructive pulmonary disease associated with biomass exposure. *Am J Respir Crit Care Med* 2014; 190: 996-1002.
10. Agusti A, Alcazar B, Cosio B, Echave JM, Faner R, Izquierdo JL, Marin JM, Soler-Cataluna JJ, Celli B, Scientific Committee of the Antes programme. Time for a change: anticipating the diagnosis and treatment of COPD. *Eur Respir J* 2020; 56.
11. Han MK, Agusti A, Celli BR, Criner GJ, Halpin DMG, Roche N, Papi A, Stockley RA, Wedzicha J, Vogelmeier CF. From GOLD 0 to Pre-COPD. *Am J Respir Crit Care Med* 2021; 203: 414-423.
12. Celli BR, Agusti A. COPD: time to improve its taxonomy? *ERJ Open Res* 2018; 4.
13. Committee GS. Global Strategy for Diagnosos, Management and Prevention of COPD. 2021 [cited 2021 September 11]. Available from: www.goldcopd.org.
14. Agusti A, Celli B. Avoiding confusion in COPD: from risk factors to phenotypes to measures of disease characterisation. *Eur Respir J* 2011; 38: 749-751.
15. Zhou Y, Zhong NS, Li X, Chen S, Zheng J, Zhao D, Yao W, Zhi R, Wei L, He B, Zhang X, Yang C, Li Y, Li F, Du J, Gui J, Hu B, Bai C, Huang P, Chen G, Xu Y, Wang C, Liang B, Li Y, Hu G, Tan H, Ye X, Ma X, Chen Y, Hu X, Tian J, Zhu X, Shi Z, Du X, Li M, Liu S, Yu R, Zhao J, Ma Q, Xie C, Li X, Chen T, Lin Y, Zeng L, Ye C, Ye W, Luo X, Zeng L, Yu S, Guan WJ, Ran P. Tiotropium in Early-Stage Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2017; 377: 923-935.
16. Agusti A, Noell G, Brugada J, Faner R. Lung function in early adulthood and health in later life: a transgenerational cohort analysis. *Lancet Respir Med* 2017; 5: 935-945.

17. Kohansal R, Martinez-Camblor P, Agusti A, Buist AS, Mannino DM, Soriano JB. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. *Am J Respir Crit Care Med* 2009; 180: 3-10.
18. Colak Y, Afzal S, Nordestgaard BG, Vestbo J, Lange P. Prevalence, Characteristics, and Prognosis of Early Chronic Obstructive Pulmonary Disease. The Copenhagen General Population Study. *Am J Respir Crit Care Med* 2020; 201: 671-680.
19. Morice AH, Celli B, Kesten S, Lystig T, Tashkin D, Decramer M. COPD in young patients: a pre-specified analysis of the four-year trial of tiotropium (UPLIFT). *Respir Med* 2010; 104: 1659-1667.
20. Decramer M, Cooper CB. Treatment of COPD: the sooner the better? *Thorax* 2010; 65: 837-841.
21. Woodruff PG, Agusti A, Roche N, Singh D, Martinez FJ. Current concepts in targeting chronic obstructive pulmonary disease pharmacotherapy: making progress towards personalised management. *Lancet (London, England)* 2015; 385: 1789-1798.
22. Silverman EK, Chapman HA, Drazen JM, Weiss ST, Rosner B, Campbell EJ, O'Donnell WJ, Reilly JJ, Ginns L, Mentzer S, Wain J, Speizer FE. Genetic epidemiology of severe, early-onset chronic obstructive pulmonary disease. Risk to relatives for airflow obstruction and chronic bronchitis. *Am J Respir Crit Care Med* 1998; 157: 1770-1778.
23. Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. Combined Impact of Smoking and Early Life Exposures on Adult Lung Function Trajectories. *Am J Respir Crit Care Med* 2017.
24. Agusti A, Hogg JC. Update on the Pathogenesis of Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2019; 381: 1248-1256.
25. Wan ES, Castaldi PJ, Cho MH, Hokanson JE, Regan EA, Make BJ, Beaty TH, Han MK, Curtis JL, Curran-Everett D, Lynch DA, DeMeo DL, Crapo JD, Silverman EK, COPDGene Investigators. Epidemiology, genetics, and subtyping of preserved ratio impaired spirometry (PRISm) in COPDGene. *Respir Res* 2014; 15: 89.
26. Harvey BG, Strulovici-Barel Y, Kaner RJ, Sanders A, Vincent TL, Mezey JG, Crystal RG. Risk of COPD with obstruction in active smokers with normal spirometry and reduced diffusion capacity. *Eur Respir J* 2015; 46: 1589-1597.
27. Petersen H, Sood A, Polverino F, Owen CA, Pinto-Plata V, Celli BR, Tesfaigzi Y. The Course of Lung Function in Middle-aged Heavy Smokers: Incidence and Time to Early Onset of Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2018; 198: 1449-1451.
28. Vestbo J, Rennard S. Chronic obstructive pulmonary disease biomarker(s) for disease activity needed--urgently. *Am J Respir Crit Care Med* 2010; 182: 863-864.
29. Celli B, Locantore N, Yates JC, Bakke P, Calverley PMA, Crim C, Coxson HO, Lomas DA, MacNee W, Miller BE, Mullerova H, Rennard SI, Silverman EK, Wouters E, Tal-Singer R, Agusti A, Vestbo J, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints Investigators. Markers of disease activity in COPD: an 8-year mortality study in the ECLIPSE cohort. *Eur Respir J* 2021; 57.
30. Agusti A, Edwards LD, Rennard SI, MacNee W, Tal-Singer R, Miller BE, Vestbo J, Lomas DA, Calverley PM, Wouters E, Crim C, Yates JC, Silverman EK, Coxson HO, Bakke P, Mayer RJ, Celli B, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints Investigators. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS One* 2012; 7: e37483.

31. McDonald VM, Higgins I, Wood LG, Gibson PG. Multidimensional assessment and tailored interventions for COPD: respiratory utopia or common sense? *Thorax* 2013; 68: 691-694.
32. Dransfield MT, Kunisaki KM, Strand MJ, Anzueto A, Bhatt SP, Bowler RP, Criner GJ, Curtis JL, Hanania NA, Nath H, Putcha N, Roark SE, Wan ES, Washko GR, Wells JM, Wendt CH, Make BJ, COPDGene Investigators. Acute Exacerbations and Lung Function Loss in Smokers with and without Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2017; 195: 324-330.
33. Guerra S, Halonen M, Vasquez MM, Spangenberg A, Stern DA, Morgan WJ, Wright AL, Lavi I, Tares L, Carsin AE, Dobano C, Barreiro E, Zock JP, Martinez-Moratalla J, Urrutia I, Sunyer J, Keidel D, Imboden M, Probst-Hensch N, Hallberg J, Melen E, Wickman M, Bousquet J, Belgrave DC, Simpson A, Custovic A, Anto JM, Martinez FD. Relation between circulating CC16 concentrations, lung function, and development of chronic obstructive pulmonary disease across the lifespan: a prospective study. *Lancet Respir Med* 2015; 3: 613-620.
34. Zhai J, Stern DA, Sherrill DL, Spangenberg AL, Wright AL, Morgan WJ, Halonen M, Martinez FD, Guerra S. Trajectories and Early Determinants of Circulating CC16 from Birth to Age 32 Years. *Am J Respir Crit Care Med* 2018; 198: 267-270.
35. Melen E, Guerra S. Recent advances in understanding lung function development. *F1000Res* 2017; 6: 726.
36. Melen E, Koppelman GH, Guerra S. On Genetics, Lung Developmental Biology, and Adult Lung Function. *Am J Respir Crit Care Med* 2020; 202: 791-793.
37. Cosio BG, Pascual-Guardia S, Borras-Santos A, Peces-Barba G, Santos S, Vigil L, Soler-Cataluna JJ, Martinez-Gonzalez C, Casanova C, Marcos PJ, Alvarez CJ, Lopez-Campos JL, Gea J, Garcia-Aymerich J, Molina J, Roman M, Moises J, Szabo V, Reagan EA, San Jose Estepar R, Washko G, Agusti A, Faner R. Phenotypic characterisation of early COPD: a prospective case-control study. *ERJ Open Res* 2020; 6.
38. Sanchez-Salcedo P, Divo M, Casanova C, Pinto-Plata V, de-Torres JP, Cote C, Cabrera C, Zagaceta J, Rodriguez-Roisin R, Zulueta JJ, Marin JM, Celli B. Disease progression in young patients with COPD: rethinking the Fletcher and Peto model. *Eur Respir J* 2014; 44: 324-331.
39. Dransfield M, Stolz D, Kleinert S, Lancet COPD Commissioners. Towards eradication of chronic obstructive pulmonary disease: a Lancet Commission. *Lancet (London, England)* 2019; 393: 1786-1788.
40. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, Decramer M, UPLIFT. Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 1543-1554.
41. Rabe KF, Martinez FJ, Ferguson GT, Wang C, Singh D, Wedzicha JA, Trivedi R, St Rose E, Ballal S, McLaren J, Darken P, Aurivillius M, Reisner C, Dorinsky P, ETHOS Investigators. Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD. *N Engl J Med* 2020; 383: 35-48.
42. Lipson DA, Crim C, Criner GJ, Day NC, Dransfield MT, Halpin DMG, Han MK, Jones CE, Kilbride S, Lange P, Lomas DA, Lettis S, Manchester P, Martin N, Midwinter D, Morris A, Pascoe SJ, Singh D, Wise RA, Martinez FJ. Reduction in All-Cause Mortality with Fluticasone Furoate/Umeclidinium/Vilanterol in Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2020; 201: 1508-1516.

43. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J, TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356: 775-789.
44. Wang C, Xu J, Yang L, Xu Y, Zhang X, Bai C, Kang J, Ran P, Shen H, Wen F, Huang K, Yao W, Sun T, Shan G, Yang T, Lin Y, Wu S, Zhu J, Wang R, Shi Z, Zhao J, Ye X, Song Y, Wang Q, Zhou Y, Ding L, Yang T, Chen Y, Guo Y, Xiao F, Lu Y, Peng X, Zhang B, Xiao D, Chen CS, Wang Z, Zhang H, Bu X, Zhang X, An L, Zhang S, Cao Z, Zhan Q, Yang Y, Cao B, Dai H, Liang L, He J, China Pulmonary Health Study Group. Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): a national cross-sectional study. *Lancet (London, England)* 2018; 391: 1706-1717.
45. Force USPST, Siu AL, Bibbins-Domingo K, Grossman DC, Davidson KW, Epling JW, Jr., Garcia FA, Gillman M, Kemper AR, Krist AH, Kurth AE, Landefeld CS, Mangione CM, Harper DM, Phillips WR, Phipps MG, Pignone MP. Screening for Chronic Obstructive Pulmonary Disease: US Preventive Services Task Force Recommendation Statement. *JAMA* 2016; 315: 1372-1377.
46. Martinez FJ, O'Connor GT. Screening, Case-Finding, and Outcomes for Adults With Unrecognized COPD. *JAMA* 2016; 315: 1343-1344.
47. Agusti A, Fabbri LM, Baraldi E, Celli B, Corradi M, Faner R, Martinez FD, Melen E, Papi A. Spirometry: A practical lifespan predictor of global health and chronic respiratory and non-respiratory diseases. *Eur J Intern Med* 2021; 89: 3-9.
48. Martinez FJ, Raczek AE, Seifer FD, Conoscenti CS, Curtice TG, D'Eletto T, Cote C, Hawkins C, Phillips AL, COPD-PS Clinician Working Group. Development and initial validation of a self-scored COPD Population Screener Questionnaire (COPD-PS). *COPD* 2008; 5: 85-95.
49. Price DB, Tinkelman DG, Halbert RJ, Nordyke RJ, Isonaka S, Nonikov D, Juniper EF, Freeman D, Hausen T, Levy ML, Ostrem A, van der Molen T, van Schayck CP. Symptom-based questionnaire for identifying COPD in smokers. *Respiration* 2006; 73: 285-295.
50. Maples P, Franks A, Ray S, Stevens AB, Wallace LS. Development and validation of a low-literacy Chronic Obstructive Pulmonary Disease knowledge Questionnaire (COPD-Q). *Patient Educ Couns* 2010; 81: 19-22.
51. Yawn BP, Mapel DW, Mannino DM, Martinez FJ, Donohue JF, Hanania NA, Kosinski M, Rendas-Baum R, Mintz M, Samuels S, Dalal AA, Lung Function Questionnaire Working Group. Development of the Lung Function Questionnaire (LFQ) to identify airflow obstruction. *Int J Chron Obstruct Pulmon Dis* 2010; 5: 1-10.
52. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. *Eur Respir J* 2009; 34: 648-654.
53. Martinez FJ, Mannino D, Leidy NK, Malley KG, Bacci ED, Barr RG, Bowler RP, Han MK, Houfek JF, Make B, Meldrum CA, Rennard S, Thomashow B, Walsh J, Yawn BP, High-Risk Copd Screening Study Group. A New Approach for Identifying Patients with Undiagnosed Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2017; 195: 748-756.
54. Leidy NK, Martinez FJ, Malley KG, Mannino DM, Han MK, Bacci ED, Brown RW, Houfek JF, Labaki WW, Make BJ, Meldrum CA, Quezada W, Rennard S, Thomashow B, Yawn BP. Can CAPTURE be used to identify undiagnosed patients with mild-to-moderate

754 COPD likely to benefit from treatment? *Int J Chron Obstruct Pulmon Dis* 2018; 13:
755 1901-1912.
756 55. Han MK, Steenrod AW, Bacci ED, Leidy NK, Mannino DM, Thomashow BM, Barr RG,
757 Make BJ, Bowler RP, Rennard SI, Houfek JF, Yawn BP, Meldrum CA, Walsh JW,
758 Martinez FJ. Identifying Patients with Undiagnosed COPD in Primary Care Settings:
759 Insight from Screening Tools and Epidemiologic Studies. *Chronic Obstr Pulm Dis* 2015;
760 2: 103-121.
761 56. Kim V, Crapo J, Zhao H, Jones PW, Silverman EK, Comellas A, Make BJ, Criner GJ,
762 COPDGene Investigators. Comparison between an alternative and the classic definition
763 of chronic bronchitis in COPDGene. *Ann Am Thorac Soc* 2015; 12: 332-339.
764 57. Woodruff PG, Barr RG, Bleecker E, Christenson SA, Couper D, Curtis JL, Gouskova NA,
765 Hansel NN, Hoffman EA, Kanner RE, Kleerup E, Lazarus SC, Martinez FJ, Paine R, 3rd,
766 Rennard S, Tashkin DP, Han MK, Spiromics Research Group. Clinical Significance of
767 Symptoms in Smokers with Preserved Pulmonary Function. *N Engl J Med* 2016; 374:
768 1811-1821.
769 58. Miravitlles M, Soriano JB, Garcia-Rio F, Munoz L, Duran-Tauleria E, Sanchez G, Sobradillo
770 V, Ancochea J. Prevalence of COPD in Spain: impact of undiagnosed COPD on quality
771 of life and daily life activities. *Thorax* 2009; 64: 863-868.
772 59. Martinez FJ, Rabe KF, Calverley PMA, Fabbri LM, Sethi S, Pizzichini E, McIvor A,
773 Anzueto A, Alagappan VKT, Siddiqui S, Reisner C, Zetterstrand S, Roman J,
774 Purkayastha D, Bagul N, Rennard SI. Determinants of Response to Roflumilast in Severe
775 Chronic Obstructive Pulmonary Disease. Pooled Analysis of Two Randomized Trials.
776 *Am J Respir Crit Care Med* 2018; 198: 1268-1278.
777 60. Van Remoortel H, Hornikx M, Langer D, Burtin C, Everaerts S, Verhamme P, Boonen S,
778 Gosselink R, Decramer M, Troosters T, Janssens W. Risk factors and comorbidities in
779 the preclinical stages of chronic obstructive pulmonary disease. *Am J Respir Crit Care*
780 *Med* 2014; 189: 30-38.
781 61. Garcia-Aymerich J, Puhan MA, Corriol-Rohou S, de Jong C, Demeyer H, Dobbels F, Erzen
782 D, Frei A, Gimeno-Santos E, Hopkinson NS, Ivanoff N, Karlsson N, Louvaris Z, Polkey
783 MI, Rabinovich RA, Scuri M, Tabberer M, Vogiatzis I, Troosters T, PROactive
784 consortium. Validity and responsiveness of the Daily- and Clinical visit-PROactive
785 Physical Activity in COPD (D-PPAC and C-PPAC) instruments. *Thorax* 2021; 76: 228-
786 238.
787 62. Ray E, Culliford D, Kruk H, Gillett K, North M, Astles CM, Hicks A, Johnson M, Lin SX,
788 Orlando R, Thomas M, Jordan RE, Price D, Konstantin M, Wilkinson TMA. Specialist
789 respiratory outreach: a case-finding initiative for identifying undiagnosed COPD in
790 primary care. *NPJ Prim Care Respir Med* 2021; 31: 7.
791 63. Jones RC, Price D, Ryan D, Sims EJ, von Ziegenweidt J, Mascarenhas L, Burden A, Halpin
792 DM, Winter R, Hill S, Kearney M, Holton K, Moger A, Freeman D, Chisholm A,
793 Bateman ED, Respiratory Effectiveness Group. Opportunities to diagnose chronic
794 obstructive pulmonary disease in routine care in the UK: a retrospective study of a
795 clinical cohort. *Lancet Respir Med* 2014; 2: 267-276.
796 64. Park JJH, Siden E, Zoratti MJ, Dron L, Harari O, Singer J, Lester RT, Thorlund K, Mills EJ.
797 Systematic review of basket trials, umbrella trials, and platform trials: a landscape
798 analysis of master protocols. *Trials* 2019; 20: 572.

65. Marshall E. BIOTECHNOLOGY:Disease Group Invests in Do-It-Yourself Drugs. *Science* 2000; 288: 1715b-1717b.
66. Simmons MS, Connett JE, Nides MA, Lindgren PG, Kleerup EC, Murray RP, Bjornson WM, Tashkin DP. Smoking reduction and the rate of decline in FEV(1): results from the Lung Health Study. *Eur Respir J* 2005; 25: 1011-1017.
67. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE, Lung Health Study Research G. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med* 2005; 142: 233-239.
68. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, Conway WA, Jr., Enright PL, Kanner RE, O'Hara P, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *JAMA* 1994; 272: 1497-1505.
69. Choi HK, Ataucuri-Vargas J, Lin C, Singrey A. The current state of tobacco cessation treatment. *Cleve Clin J Med* 2021; 88: 393-404.
70. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. *Lancet (London, England)* 2009; 374: 733-743.
71. Hamberger ES, Halpern-Felsher B. Vaping in adolescents: epidemiology and respiratory harm. *Curr Opin Pediatr* 2020; 32: 378-383.
72. Alter P, Baker JR, Dauletbaev N, Donnelly LE, Pistenmaa C, Schmeck B, Washko G, Vogelmeier CF. Update in Chronic Obstructive Pulmonary Disease 2019. *Am J Respir Crit Care Med* 2020; 202: 348-355.
73. Schraufnagel DE, Balmes JR, Cowl CT, De Matteis S, Jung SH, Mortimer K, Perez-Padilla R, Rice MB, Riojas-Rodriguez H, Sood A, Thurston GD, To T, Vanker A, Wuebbles DJ. Air Pollution and Noncommunicable Diseases: A Review by the Forum of International Respiratory Societies' Environmental Committee, Part 1: The Damaging Effects of Air Pollution. *Chest* 2019; 155: 409-416.
74. Thurston GD, Balmes JR, Garcia E, Gilliland FD, Rice MB, Schikowski T, Van Winkle LS, Annesi-Maesano I, Burchard EG, Carlsten C, Harkema JR, Khreis H, Kleeberger SR, Kodavanti UP, London SJ, McConnell R, Peden DB, Pinkerton KE, Reibman J, White CW. Outdoor Air Pollution and New-Onset Airway Disease. An Official American Thoracic Society Workshop Report. *Ann Am Thorac Soc* 2020; 17: 387-398.
75. Perez-Padilla R, Regalado J, Vedal S, Pare P, Chapela R, Sansores R, Selman M. Exposure to biomass smoke and chronic airway disease in Mexican women. A case-control study. *Am J Respir Crit Care Med* 1996; 154: 701-706.
76. Bruce N, Perez-Padilla R, Albalak R. Indoor air pollution in developing countries: a major environmental and public health challenge. *Bull World Health Organ* 2000; 78: 1078-1092.
77. Ramirez-Venegas A, Sansores RH, Perez-Padilla R, Regalado J, Velazquez A, Sanchez C, Mayar ME. Survival of patients with chronic obstructive pulmonary disease due to biomass smoke and tobacco. *Am J Respir Crit Care Med* 2006; 173: 393-397.
78. Regalado J, Perez-Padilla R, Sansores R, Paramo Ramirez JI, Brauer M, Pare P, Vedal S. The effect of biomass burning on respiratory symptoms and lung function in rural Mexican women. *Am J Respir Crit Care Med* 2006; 174: 901-905.
79. Olloquequi J, Jaime S, Parra V, Cornejo-Cordova E, Valdivia G, Agusti A, Silva OR. Comparative analysis of COPD associated with tobacco smoking, biomass smoke exposure or both. *Respir Res* 2018; 19: 13.

80. Walsh A, Perrem L, Khashan AS, Henry MT, Ni Chroinin M. Statins versus placebo for people with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2019; 7: CD011959.
81. Polverino F, Wu TD, Rojas-Quintero J, Wang X, Mayo J, Tomchaney M, Tram J, Packard S, Zhang D, Cleveland KH, Cordoba-Lanus E, Owen CA, Fawzy A, Kinney GL, Hersh CP, Hansel NN, Doubleday K, Sauler M, Tesfaigzi Y, Ledford JG, Casanova C, Zmijewski J, Konhilas J, Langlais PR, Schnellmann R, Rahman I, McCormack M, Celli B. Metformin: Experimental and Clinical Evidence for a Potential Role in Emphysema Treatment. *Am J Respir Crit Care Med* 2021.
82. Wu TD, Fawzy A, Kinney GL, Bon J, Neupane M, Tejwani V, Hansel NN, Wise RA, Putcha N, McCormack MC. Metformin use and respiratory outcomes in asthma-COPD overlap. *Respir Res* 2021; 22: 70.
83. Vestbo J, Lange P. Natural history of COPD: Focusing on change in FEV1. *Respirology* 2016; 21: 34-43.
84. Celli BR, Anderson JA, Cowans NJ, Crim C, Hartley BF, Martinez FJ, Morris AN, Quasny H, Yates J, Vestbo J, Calverley PMA. Pharmacotherapy and Lung Function Decline in Patients with Chronic Obstructive Pulmonary Disease. A Systematic Review. *Am J Respir Crit Care Med* 2021; 203: 689-698.
85. Burrows B. An overview of obstructive lung diseases. *Med Clin North Am* 1981; 65: 455-471.
86. Kerstjens HA, Rijcken B, Schouten JP, Postma DS. Decline of FEV1 by age and smoking status: facts, figures, and fallacies. *Thorax* 1997; 52: 820-827.
87. Zafari Z, Sin DD, Postma DS, Lofdahl CG, Vonk J, Bryan S, Lam S, Tammemagi CM, Khakban R, Man SFP, Tashkin D, Wise RA, Connett JE, McManus B, Ng R, Hollander Z, Sadatsafavi M. Individualized prediction of lung-function decline in chronic obstructive pulmonary disease. *CMAJ* 2016; 188: 1004-1011.
88. Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. The Presence of Chronic Mucus Hypersecretion across Adult Life in Relation to Chronic Obstructive Pulmonary Disease Development. *Am J Respir Crit Care Med* 2016; 193: 662-672.
89. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002; 57: 847-852.
90. Agency. EM. Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials. ICH E9.; 2020.
91. Bhatt SP, Bhakta NR, Wilson CG, Cooper CB, Barjaktarevic I, Bodduluri S, Kim YI, Eberlein M, Woodruff PG, Sciurba FC, Castaldi PJ, Han MK, Dransfield MT, Nakhmani A. New Spirometry Indices for Detecting Mild Airflow Obstruction. *Sci Rep* 2018; 8: 17484.
92. Dominelli PB, Foster GE, Guenette JA, Haverkamp HC, Eves ND, Dominelli GS, Henderson WR, O'Donnell DE, Sheel AW. Quantifying the shape of the maximal expiratory flow-volume curve in mild COPD. *Respir Physiol Neurobiol* 2015; 219: 30-35.
93. Topalovic M, Exadaktylos V, Decramer M, Troosters T, Berckmans D, Janssens W. Modelling the dynamics of expiratory airflow to describe chronic obstructive pulmonary disease. *Med Biol Eng Comput* 2014; 52: 997-1006.
94. Jones PW, Tabberer M, Chen WH. Creating scenarios of the impact of COPD and their relationship to COPD Assessment Test (CAT) scores. *BMC Pulm Med* 2011; 11: 42.

95. Raghavan N, Lam YM, Webb KA, Guenette JA, Amornputtisathaporn N, Raghavan R, Tan WC, Bourbeau J, O'Donnell DE. Components of the COPD Assessment Test (CAT) associated with a diagnosis of COPD in a random population sample. *COPD* 2012; 9: 175-183.
96. Nishimura K, Mitsuma S, Kobayashi A, Yanagida M, Nakayasu K, Hasegawa Y, Jones PW. COPD and disease-specific health status in a working population. *Respir Res* 2013; 14: 61.
97. Vogelmeier CF, Kerwin EM, Bjermer LH, Tombs L, Jones PW, Boucot IH, Naya IP, Lipson DA, Compton C, Barnes N, Maltais F. Impact of baseline COPD symptom severity on the benefit from dual versus mono-bronchodilators: an analysis of the EMAX randomised controlled trial. *Ther Adv Respir Dis* 2020; 14: 1753466620968500.
98. Gagnon P, Saey D, Provencher S, Milot J, Bourbeau J, Tan WC, Martel S, Maltais F. Walking exercise response to bronchodilation in mild COPD: a randomized trial. *Respir Med* 2012; 106: 1695-1705.
99. O'Donnell DE, Laveneziana P, Ora J, Webb KA, Lam YM, Ofir D. Evaluation of acute bronchodilator reversibility in patients with symptoms of GOLD stage I COPD. *Thorax* 2009; 64: 216-223.
100. Jones PW, Beeh KM, Chapman KR, Decramer M, Mahler DA, Wedzicha JA. Minimal clinically important differences in pharmacological trials. *Am J Respir Crit Care Med* 2014; 189: 250-255.
101. Jones PW, Gelhorn H, Wilson H, Karlsson N, Menjoge S, Mullerova H, Rennard SI, Tal-Singer R, Merrill D, Tabberer M. Responder Analyses for Treatment Effects in COPD Using the St George's Respiratory Questionnaire. *Chronic Obstr Pulm Dis* 2017; 4: 124-131.
102. Colak Y, Afzal S, Nordestgaard BG, Lange P, Vestbo J. Importance of Early COPD In Young Adults for Development of Clinical COPD: Findings from the Copenhagen General Population Study. *Am J Respir Crit Care Med* 2020.
103. Bouza E, Alvar A, Almagro P, Alonso T, Ancochea J, Barbe F, Corbella J, Gracia D, Mascaros E, Melis J, Miravitlles M, Pastor M, Perez P, Rudilla D, Torres A, Soriano JB, Vallano A, Vargas F, Palomo E. Chronic obstructive pulmonary disease (COPD) in Spain and the different aspects of its social impact: a multidisciplinary opinion document. *Rev Esp Quimioter* 2020; 33: 49-67.
104. Colak Y, Nordestgaard BG, Vestbo J, Lange P, Afzal S. Outcomes consequent to "early" COPD for interventional studies. *Eur Respir J* 2020; 55.
105. Colak Y, Nordestgaard BG, Vestbo J, Lange P, Afzal S. Comparison of five major airflow limitation criteria to identify high-risk individuals with COPD: a contemporary population-based cohort. *Thorax* 2020; 75: 944-954.
106. Scioscia G, Blanco I, Arismendi E, Burgos F, Gistau C, Foschino Barbaro MP, Celli B, O'Donnell DE, Agusti A. Different dyspnoea perception in COPD patients with frequent and infrequent exacerbations. *Thorax* 2017; 72: 117-121.
107. Regan EA, Lynch DA, Curran-Everett D, Curtis JL, Austin JH, Grenier PA, Kauczor HU, Bailey WC, DeMeo DL, Casaburi RH, Friedman P, Van Beek EJ, Hokanson JE, Bowler RP, Beaty TH, Washko GR, Han MK, Kim V, Kim SS, Yagihashi K, Washington L, McEvoy CE, Tanner C, Mannino DM, Make BJ, Silverman EK, Crapo JD, Genetic Epidemiology of COPD Investigators. Clinical and Radiologic Disease in Smokers With Normal Spirometry. *JAMA Intern Med* 2015; 175: 1539-1549.

108. Mohamed Hoesein FA, de Jong PA, Lammers JW, Mali WP, Schmidt M, de Koning HJ, van der Aalst C, Oudkerk M, Vliegenthart R, Groen HJ, van Ginneken B, van Rikxoort EM, Zanen P. Airway wall thickness associated with forced expiratory volume in 1 second decline and development of airflow limitation. *Eur Respir J* 2015; 45: 644-651.
109. Oelsner EC, Smith BM, Hoffman EA, Kalhan R, Donohue KM, Kaufman JD, Nguyen JN, Manichaikul AW, Rotter JI, Michos ED, Jacobs DR, Jr., Burke GL, Folsom AR, Schwartz JE, Watson K, Barr RG. Prognostic Significance of Large Airway Dimensions on Computed Tomography in the General Population. The Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study. *Ann Am Thorac Soc* 2018; 15: 718-727.
110. Charbonnier JP, Pompe E, Moore C, Humphries S, van Ginneken B, Make B, Regan E, Crapo JD, van Rikxoort EM, Lynch DA, COPDGene investigators. Airway wall thickening on CT: Relation to smoking status and severity of COPD. *Respir Med* 2019; 146: 36-41.
111. Pompe E, van Rikxoort EM, Mets OM, Charbonnier JP, Kuhnigk JM, de Koning HJ, Oudkerk M, Vliegenthart R, Zanen P, Lammers JJ, van Ginneken B, de Jong PA, Mohamed Hoesein FAA. Follow-up of CT-derived airway wall thickness: Correcting for changes in inspiration level improves reliability. *Eur J Radiol* 2016; 85: 2008-2013.
112. Galban CJ, Han MK, Boes JL, Chughtai KA, Meyer CR, Johnson TD, Galban S, Rehemtulla A, Kazerooni EA, Martinez FJ, Ross BD. Computed tomography-based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression. *Nat Med* 2012; 18: 1711-1715.
113. Bhatt SP, Soler X, Wang X, Murray S, Anzueto AR, Beaty TH, Boriek AM, Casaburi R, Criner GJ, Diaz AA, Dransfield MT, Curran-Everett D, Galban CJ, Hoffman EA, Hogg JC, Kazerooni EA, Kim V, Kinney GL, Lagstein A, Lynch DA, Make BJ, Martinez FJ, Ramsdell JW, Reddy R, Ross BD, Rossiter HB, Steiner RM, Strand MJ, van Beek EJ, Wan ES, Washko GR, Wells JM, Wendt CH, Wise RA, Silverman EK, Crapo JD, Bowler RP, Han MK, COPDGene Investigators. Association between Functional Small Airway Disease and FEV1 Decline in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2016; 194: 178-184.
114. Bodduluri S, Reinhardt JM, Hoffman EA, Newell JD, Jr., Nath H, Dransfield MT, Bhatt SP, COPDGene Investigators. Signs of Gas Trapping in Normal Lung Density Regions in Smokers. *Am J Respir Crit Care Med* 2017; 196: 1404-1410.
115. Kirby M, Tanabe N, Vasilescu DM, Cooper JD, McDonough JE, Verleden SE, Vanaudenaerde BM, Sin DD, Tan WC, Coxson HO, Hogg JC. Computed Tomography Total Airway Count Is Associated with the Number of Micro-Computed Tomography Terminal Bronchioles. *Am J Respir Crit Care Med* 2020; 201: 613-615.
116. Kirby M, Tanabe N, Tan WC, Zhou G, Obeidat M, Hague CJ, Leipsic J, Bourbeau J, Sin DD, Hogg JC, Coxson HO, Canadian Respiratory Research Network, CanCold Collaborative Research Group. Total Airway Count on Computed Tomography and the Risk of Chronic Obstructive Pulmonary Disease Progression. Findings from a Population-based Study. *Am J Respir Crit Care Med* 2018; 197: 56-65.
117. Bodduluri S, Puliyakote ASK, Gerard SE, Reinhardt JM, Hoffman EA, Newell JD, Jr., Nath HP, Han MK, Washko GR, San Jose Estepar R, Dransfield MT, Bhatt SP, COPDGene Investigators. Airway fractal dimension predicts respiratory morbidity and mortality in COPD. *J Clin Invest* 2018; 128: 5374-5382.

982 118. Bodduluri S, Kizhakke Puliyakote A, Nakhmani A, Charbonnier JP, Reinhardt JM, Bhatt
983 SP. Computed Tomography-based Airway Surface Area-to-Volume Ratio for
984 Phenotyping Airway Remodeling in Chronic Obstructive Pulmonary Disease. *Am J*
985 *Respir Crit Care Med* 2021; 203: 185-191.
986 119. Bodduluri S, Nakhmani A, Reinhardt JM, Wilson CG, McDonald ML, Rudraraju R, Jaeger
987 BC, Bhakta NR, Castaldi PJ, Sciurba FC, Zhang C, Bangalore PV, Bhatt SP. Deep neural
988 network analyses of spirometry for structural phenotyping of chronic obstructive
989 pulmonary disease. *JCI Insight* 2020; 5.
990 120. Mohamed Hoesein FA, de Hoop B, Zanen P, Gietema H, Kruitwagen CL, van Ginneken B,
991 Isgum I, Mol C, van Klaveren RJ, Dijkstra AE, Groen HJ, Boezen HM, Postma DS,
992 Prokop M, Lammers JW. CT-quantified emphysema in male heavy smokers: association
993 with lung function decline. *Thorax* 2011; 66: 782-787.
994 121. Washko GR, Kinney GL, Ross JC, San Jose Estepar R, Han MK, Dransfield MT, Kim V,
995 Hatabu H, Come CE, Bowler RP, Silverman EK, Crapo J, Lynch DA, Hokanson J, Diaz
996 AA, COPDGene Investigators. Lung Mass in Smokers. *Acad Radiol* 2017; 24: 386-392.
997 122. Haruna A, Muro S, Nakano Y, Ohara T, Hoshino Y, Ogawa E, Hirai T, Niimi A, Nishimura
998 K, Chin K, Mishima M. CT scan findings of emphysema predict mortality in COPD.
999 *Chest* 2010; 138: 635-640.
1000 123. Johannessen A, Skorge TD, Bottai M, Grydeland TB, Nilsen RM, Coxson H, Dirksen A,
1001 Omenaas E, Gulsvik A, Bakke P. Mortality by level of emphysema and airway wall
1002 thickness. *Am J Respir Crit Care Med* 2013; 187: 602-608.
1003 124. Lynch DA, Moore CM, Wilson C, Nevrekar D, Jennermann T, Humphries SM, Austin
1004 JHM, Grenier PA, Kauczor HU, Han MK, Regan EA, Make BJ, Bowler RP, Beaty TH,
1005 Curran-Everett D, Hokanson JE, Curtis JL, Silverman EK, Crapo JD, Genetic
1006 Epidemiology of COPD Investigators. CT-based Visual Classification of Emphysema:
1007 Association with Mortality in the COPDGene Study. *Radiology* 2018; 288: 859-866.
1008 125. Bodduluri S, Bhatt SP, Hoffman EA, Newell JD, Jr., Martinez CH, Dransfield MT, Han
1009 MK, Reinhardt JM, COPDGene Investigators. Biomechanical CT metrics are associated
1010 with patient outcomes in COPD. *Thorax* 2017; 72: 409-414.
1011 126. Mohamed Hoesein FA, Zanen P, de Jong PA, van Ginneken B, Boezen HM, Groen HJ,
1012 Oudkerk M, de Koning HJ, Postma DS, Lammers JW. Rate of progression of CT-
1013 quantified emphysema in male current and ex-smokers: a follow-up study. *Respir Res*
1014 2013; 14: 55.
1015 127. Pompe E, Moore CM, Mohamed Hoesein FAA, de Jong PA, Charbonnier JP, Han MK,
1016 Humphries SM, Hatt CR, Galban CJ, Silverman EK, Crapo JD, Washko GR, Regan EA,
1017 Make B, Strand M, Lammers JJ, van Rikxoort EM, Lynch DA, COPDGene investigators.
1018 Progression of Emphysema and Small Airways Disease in Cigarette Smokers. *Chronic*
1019 *Obstr Pulm Dis* 2020.
1020 128. Stockley RA, Parr DG, Piitulainen E, Stolk J, Stoel BC, Dirksen A. Therapeutic efficacy of
1021 alpha-1 antitrypsin augmentation therapy on the loss of lung tissue: an integrated analysis
1022 of 2 randomised clinical trials using computed tomography densitometry. *Respir Res*
1023 2010; 11: 136.
1024 129. Chapman KR, Burdon JG, Piitulainen E, Sandhaus RA, Seersholm N, Stocks JM, Stoel BC,
1025 Huang L, Yao Z, Edelman JM, McElvaney NG, Rapid Trial Study Group. Intravenous
1026 augmentation treatment and lung density in severe alpha1 antitrypsin deficiency

(RAPID): a randomised, double-blind, placebo-controlled trial. *Lancet (London, England)* 2015; 386: 360-368.
130. Thomsen LH, Shaker SB, Dirksen A, Pedersen JH, Tal-Singer R, Bakke P, Vestbo J. Correlation Between Emphysema and Lung Function in Healthy Smokers and Smokers With COPD. *Chronic Obstr Pulm Dis* 2015; 2: 204-213.
131. Coxson HO, Dirksen A, Edwards LD, Yates JC, Agusti A, Bakke P, Calverley PM, Celli B, Crim C, Duvoix A, Fauerbach PN, Lomas DA, Macnee W, Mayer RJ, Miller BE, Muller NL, Rennard SI, Silverman EK, Tal-Singer R, Wouters EF, Vestbo J, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints Investigators. The presence and progression of emphysema in COPD as determined by CT scanning and biomarker expression: a prospective analysis from the ECLIPSE study. *Lancet Respir Med* 2013; 1: 129-136.
132. Boes JL, Hoff BA, Bule M, Johnson TD, Rehemtulla A, Chamberlain R, Hoffman EA, Kazerooni EA, Martinez FJ, Han MK, Ross BD, Galban CJ. Parametric response mapping monitors temporal changes on lung CT scans in the subpopulations and intermediate outcome measures in COPD Study (SPIROMICS). *Acad Radiol* 2015; 22: 186-194.
133. Bastarrika G, Wisnivesky JP, Pueyo JC, Diaz L, Arraiza M, Villanueva A, Alcaide AB, Campo A, Seijo L, de Torres JP, Zulueta JJ. Low-dose volumetric computed tomography for quantification of emphysema in asymptomatic smokers participating in an early lung cancer detection trial. *J Thorac Imaging* 2009; 24: 206-211.
134. Vasilescu DM, Martinez FJ, Marchetti N, Galban CJ, Hatt C, Meldrum CA, Dass C, Tanabe N, Reddy RM, Lagstein A, Ross BD, Labaki WW, Murray S, Meng X, Curtis JL, Hackett TL, Kazerooni EA, Criner GJ, Hogg JC, Han MK. Noninvasive Imaging Biomarker Identifies Small Airway Damage in Severe Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2019; 200: 575-581.
135. Bhatt SP, Bodduluri S, Hoffman EA, Newell JD, Jr., Sieren JC, Dransfield MT, Reinhardt JM, COPDGene Investigators. Computed Tomography Measure of Lung at Risk and Lung Function Decline in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2017; 196: 569-576.
136. Dunican EM, Elicker BM, Henry T, Gierada DS, Schiebler ML, Anderson W, Barjaktarevic I, Barr RG, Bleecker ER, Boucher RC, Bowler R, Christenson SA, Comellas A, Cooper CB, Couper D, Criner GJ, Dransfield M, Doerschuk CM, Drummond MB, Hansel NN, Han MK, Hastie AT, Hoffman EA, Krishnan JA, Lazarus SC, Martinez FJ, McCulloch CE, O'Neal WK, Ortega VE, Paine R, 3rd, Peters S, Schroeder JD, Woodruff PG, Fahy JV. Mucus Plugs and Emphysema in the Pathophysiology of Airflow Obstruction and Hypoxemia in Smokers. *Am J Respir Crit Care Med* 2021; 203: 957-968.
137. Stewart NJ, Smith LJ, Chan HF, Eaden JA, Rajaram S, Swift AJ, Weatherley ND, Biancardi A, Collier GJ, Hughes D, Klafkowski G, Johns CS, West N, Ugonna K, Bianchi SM, Lawson R, Sabroe I, Marshall H, Wild JM. Lung MRI with hyperpolarised gases: current & future clinical perspectives. *The British journal of radiology* 2021: 20210207.
138. Vestbo J, Anderson JA, Brook RD, Calverley PM, Celli BR, Crim C, Martinez F, Yates J, Newby DE, Summit Investigators. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *Lancet (London, England)* 2016; 387: 1817-1826.

139. Kochanek KD, Murphy SL, Xu J, Arias E. Deaths: Final Data for 2017. *Natl Vital Stat Rep* 2019; 68: 1-77.
140. Celli BR, Decramer M, Liu D, Metzdorf N, Asijee GM, Tashkin DP. Defining a COPD composite safety endpoint for demonstrating efficacy in clinical trials: results from the randomized, placebo-controlled UPLIFT(R) trial. *Respir Res* 2016; 17: 48.
141. Singh D, Criner GJ, Naya I, Jones PW, Tombs L, Lipson DA, Han MK. Measuring disease activity in COPD: is clinically important deterioration the answer? *Respir Res* 2020; 21: 134.
142. Naya I, Compton C, Ismaila AS, Birk R, Brealey N, Tabberer M, Zhu CQ, Lipson DA, Criner G. Preventing clinically important deterioration with single-inhaler triple therapy in COPD. *ERJ Open Res* 2018; 4.
143. Naya IP, Tombs L, Lipson DA, Compton C. Preventing Clinically Important Deterioration of COPD with Addition of Umeclidinium to Inhaled Corticosteroid/Long-Acting beta2-Agonist Therapy: An Integrated Post Hoc Analysis. *Adv Ther* 2018; 35: 1626-1638.
144. Singh D, Maleki-Yazdi MR, Tombs L, Iqbal A, Fahy WA, Naya I. Prevention of clinically important deteriorations in COPD with umeclidinium/vilanterol. *Int J Chron Obstruct Pulmon Dis* 2016; 11: 1413-1424.
145. Rabe KF, Halpin DMG, Han MK, Miravitlles M, Singh D, Gronke L, Voss F, Martinez FJ. Composite endpoints in COPD: clinically important deterioration in the UPLIFT trial. *Respir Res* 2020; 21: 177.
146. Naya IP, Tombs L, Muellerova H, Compton C, Jones PW. Long-term outcomes following first short-term clinically important deterioration in COPD. *Respir Res* 2018; 19: 222.
147. Han MK, Criner GJ, Dransfield MT, Halpin DMG, Jones CE, Kilbride S, Lange P, Lettis S, Lipson DA, Lomas DA, Martin N, Martinez FJ, Wise RA, Naya IP, Singh D. Prognostic value of clinically important deterioration in COPD: IMPACT trial analysis. *ERJ Open Res* 2021; 7.
148. Kostikas K, Mackay AJ, Vogelmeier CF, Frent SM, Gupta P, Banerji D, Patalano F, Pfister PJ, Wedzicha JA. Early Clinically Important Improvement (ECII) and Exacerbation Outcomes in COPD Patients. *Int J Chron Obstruct Pulmon Dis* 2020; 15: 1831-1838.
149. Vogelmeier CF, Fuhlbrigge A, Jauhiainen A, Scheepers L, Bengtsson T, Peterson S, Karlsson N, Sethi T, Locantore N, Tal-Singer R, Rennard S, Fageras M, Da Silva CA. COPDCompEx: A novel composite endpoint for COPD exacerbations to enable faster clinical development. *Respir Med* 2020; 173: 106175.
150. Lawrence Gould A, Boye ME, Crowther MJ, Ibrahim JG, Quartey G, Micallef S, Bois FY. Joint modeling of survival and longitudinal non-survival data: current methods and issues. Report of the DIA Bayesian joint modeling working group. *Stat Med* 2015; 34: 2181-2195.
151. Ibrahim JG, Chu H, Chen LM. Basic concepts and methods for joint models of longitudinal and survival data. *J Clin Oncol* 2010; 28: 2796-2801.
152. Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, Humbert M, Jones P, Gibson PG, Vestbo J, Beasley R, Pavord ID. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J* 2016; 47: 410-419.
153. Singh D, Bafadhel M, Brightling CE, Sciurba FC, Curtis JL, Martinez FJ, Pasquale CB, Merrill DD, Metzdorf N, Petruzzelli S, Tal-Singer R, Compton C, Rennard S, Martin UJ. Blood Eosinophil Counts in Clinical Trials for Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2020; 202: 660-671.

154. Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Criner GJ, Frith P, Halpin DMG, Han M, Lopez Varela MV, Martinez F, Montes de Oca M, Papi A, Pavord ID, Roche N, Sin DD, Stockley R, Vestbo J, Wedzicha JA, Vogelmeier C. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: the GOLD science committee report 2019. *Eur Respir J* 2019; 53.
155. Higham A, Beech A, Wolosianka S, Jackson N, Long G, Kolsum U, Southworth T, Pham TH, Sridhar S, McCrae C, Newbold P, Singh D. Type 2 inflammation in eosinophilic chronic obstructive pulmonary disease. *Allergy* 2021; 76: 1861-1864.
156. George L, Taylor AR, Esteve-Codina A, Soler Artigas M, Thun GA, Bates S, Pavlidis S, Wagers S, Boland A, Prasse A, Boschetto P, Parr DG, Nowinski A, Barta I, Hohlfeld J, Greulich T, van den Berge M, Hiemstra PS, Timens W, Hinks T, Wenzel S, Siddiqui S, Richardson M, Venge P, Heath S, Gut I, Tobin MD, Edwards L, Riley JH, Djukanovic R, Auffray C, De-Meulder B, Erik-Dahlen S, Adcock IM, Chung KF, Ziegler-Heitbrock L, Sterk PJ, Singh D, Brightling CE, U B, the Ev Ast. Blood eosinophil count and airway epithelial transcriptome relationships in COPD versus asthma. *Allergy* 2020; 75: 370-380.
157. Beech AS, Lea S, Kolsum U, Wang Z, Miller BE, Donaldson GC, Wedzicha JA, Brightling CE, Singh D. Bacteria and sputum inflammatory cell counts; a COPD cohort analysis. *Respir Res* 2020; 21: 289.
158. Wang Z, Locantore N, Haldar K, Ramsheh MY, Beech AS, Ma W, Brown JR, Tal-Singer R, Barer MR, Bafadhel M, Donaldson GC, Wedzicha JA, Singh D, Wilkinson TMA, Miller BE, Brightling CE. Inflammatory Endotype-associated Airway Microbiome in Chronic Obstructive Pulmonary Disease Clinical Stability and Exacerbations: A Multicohort Longitudinal Analysis. *Am J Respir Crit Care Med* 2021; 203: 1488-1502.
159. Martinez-Garcia MA, Faner R, Oscullo G, de la Rosa D, Soler-Cataluna JJ, Ballester M, Agusti A. Inhaled Steroids, Circulating Eosinophils, Chronic Airway Infection, and Pneumonia Risk in Chronic Obstructive Pulmonary Disease. A Network Analysis. *Am J Respir Crit Care Med* 2020; 201: 1078-1085.
160. Agusti A, Faner R, Donaldson G, Heuvelin E, Breyer-Kohansal R, Melen E, Maitland-van der Zee AH, Vestbo J, Allinson JP, Vanfleteren L, van den Berge M, Adcock IM, Lahousse L, Brusselle G, Wedzicha JA, on behalf of the CADSET Clinical Research Collaboration. Chronic Airway Diseases Early Stratification (CADSET): a new ERS Clinical Research Collaboration. *Eur Respir J* 2019; 53.
161. Hizawa N, Fukunaga K, Sugiura H, Nakano Y, Kato M, Sugiyama Y, Hanazawa T, Kaise T, Tal-Singer R, Jones PW, Barnes N, Compton C, Ishii T. A Prospective Cohort Study to Assess Obstructive Respiratory Disease Phenotypes and Endotypes in Japan: The TRAIT Study Design. *Int J Chron Obstruct Pulmon Dis* 2021; 16: 1813-1822.
162. Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. *N Engl J Med* 2017; 377: 62-70.
163. Saville BR, Berry SM. Efficiencies of platform clinical trials: A vision of the future. *Clin Trials* 2016; 13: 358-366.
164. LaVange L, Adam SJ, Currier JS, Higgs ES, Reineck LA, Hughes EA, Read SW, Group AT-CW. Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV): Designing Master Protocols for Evaluation of Candidate COVID-19 Therapeutics. *Ann Intern Med* 2021.
165. Zhang W, Lv Y, Yang J, Chen Y, He Y, Huang J. Study Design Characteristics and Pharmacological Mechanisms in International Clinical Trials Registry Platform:

Registered Clinical Trials on Antiviral Drugs for COVID-19. *Drug Des Devel Ther* 2020; 14: 3803-3813.

166. Vestbo J, Sorensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet (London, England)* 1999; 353: 1819-1823.
167. Pauwels RA, Lofdahl CG, Laitinen LA, Schouten JP, Postma DS, Pride NB, Ohlsson SV. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. *N Engl J Med* 1999; 340: 1948-1953.
168. Celli BR, Thomas NE, Anderson JA, Ferguson GT, Jenkins CR, Jones PW, Vestbo J, Knobil K, Yates JC, Calverley PM. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. *Am J Respir Crit Care Med* 2008; 178: 332-338.
169. Decramer M, Rutten-van Molken M, Dekhuijzen PN, Troosters T, van Herwaarden C, Pellegrino R, van Schayck CP, Olivieri D, Del Donno M, De Backer W, Lankhorst I, Ardia A. Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. *Lancet (London, England)* 2005; 365: 1552-1560.
170. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000; 320: 1297-1303.
171. Lung Health Study Research G, Wise R, Connett J, Weinmann G, Scanlon P, Skeans M. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med* 2000; 343: 1902-1909.
172. Decramer M, Celli B, Kesten S, Lystig T, Mehra S, Tashkin DP, Uplift investigators. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. *Lancet (London, England)* 2009; 374: 1171-1178.

Table 1. Nosology used in this review. For further explanations, see text.

Term	Definition
Early COPD	*Biological* term that indicates that the disease is near its beginning (at any age); requires validated *biomarkers* to be identified/quantified in clinical practice.
Mild COPD	*Functional* term that indicates that the disease is associated with mild airflow limitation (at any age)
Young COPD	*Age-dependent* term that identifies a subpopulation of patients with COPD (FEV1/FVC<0.7) between 20-50 years of age (independent of the severity of airflow limitation present)
Pre-COPD	*Individuals* (of any age) who present chronic respiratory symptoms, with or without structural and/or functional abnormalities, in the absence of airflow limitation (FEV1/FVC>0.7) who may (or may not) develop persistent airflow limitation (i.e., COPD) over time
Disease activity	*Biological* term that relates to the level of activation of the pathobiological processes (endotypes) that cause the disease. It can ideally be identified and quantified by validated biomarkers (currently lacking in COPD)
Disease progression	*Clinical* term that refers to a progressive deterioration in an objective marker of pathology or lung function
Primary prevention	Aimed at preventing the disease *before it occurs* by eliminating exposures to risk factors and/or increasing resistance to disease should exposure occur
Secondary prevention	Aimed at reducing the impact of a disease that *has already occurred* by diagnosing and treating it as soon as possible to halt or slow its progress
Tertiary prevention	Aimed at *mitigating the impact* of an ongoing illness

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 non-normal distribution of important trial outcomes
4. Differing patterns of disease progression
5. Slow FEV_1 decline which is further compounded by dropout or death amongst 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

Table 3: Rate of FEV_1 Decline (mL/yr.) Study Results

Study	Length (years)	N	Mean FEV_1 (%)	Mean Age	Active	Placebo	Difference (95% CI)	Estimated Effective SD	Implied N/group for 90% power to detect[2]:	
									12 mL/yr. Difference	15 mL/yr. Difference
SUMMIT (138)	1-4[1]	16485	60	65	38	46	-8 (-15, -1)	154	3462	2216
Zhou et al (15)	2	841	78	64	29	51	-22 (-37, -6)	110	1766	1131
Copenhagen CLS (166)	3	290	86	59	45	42	3 (-13, 19)	69	695	445
EUROSCOPE (167)	3	1277	77	52	57	69	-12 NS	UNK		
TORCH (168)	3	6112	44	65	42/43/39	55	-16 (-25, -8)	113	1864	1193
BRONCUS (169)	3	523	57	62	56	47	8 (-10, 25)	97	1374	879
ISOLDE (170)	3	751	50	64	50	59	-9 (-3, 20)	76	843	540
Lung Health Study II (171)	3.5 - 4.5[1]	1116	68	56	44	47	-3 (-11, 5)	70	716	458
UPLIFT (40, 172)	4	5993	48	65	40	42	-2 (-6, 2)	72	757	485
Lung Health Study I (68)	5	5887	78	48	30	66	-31 UNK	57	475	304

[1] Variable length follow-up

NS – not stated; UNK - unknown

Table 4: Partnerships that may enable treatment trials in young patients.

Organization	Contribution
Professional organizations	Individuals at risk based on occupational exposure (e.g., firefighters, veterans, farm workers)
Primary care providers	Identify individuals at risk based on symptoms and risk (or early life events)
Birth cohorts (population based) with long longitudinal follow-up	Risk predictors, biomarkers, participants
Population based cohorts with longitudinal follow-up	Risk predictors, biomarkers
Pharmaceutical Industry	Partner on Platform trials, shared risk
International scientific multidisciplinary team	Collaborate on trial design and implementation
Patient Advocacy Groups	Coordinate platform trials

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 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	• Three years	• Three to five years
Interim analysis at 6 -12 months (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 (since 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 years • Biomarker enrichment†	• Individuals with NOCB symptoms as defined using the CAT or SGRQ • A Respiratory HCRU event in the past 24 months • Subjects with rapid FEV_1 decline • Biomarker enrichment†

[1] Variable length follow-up

NS – not stated; UNK – unknown

† Circulating eosinophils, microbial assessments (see text)

*such as Clinically Important Deterioration (CID) examining time to FEV_1 decline, exacerbation or symptom worsening.

Figure 1. Examples of lung-Function Trajectories from birth to death. The red shaded area highlights the population of young adults with COPD to be included in treatment trials. Grey shaded areas indicate that these age-limits are somewhat arbitrary (based on normal peak + plateau lung function), and that therefore some age variability may be acceptable. Note also that this age range includes trajectories with normal peak lung function (100% ref) as well as those with reduced peak lung function (<80% ref.) and that both can have a normal (stable) or an enhanced decline with time (progressive disease) For further explanations, see text.

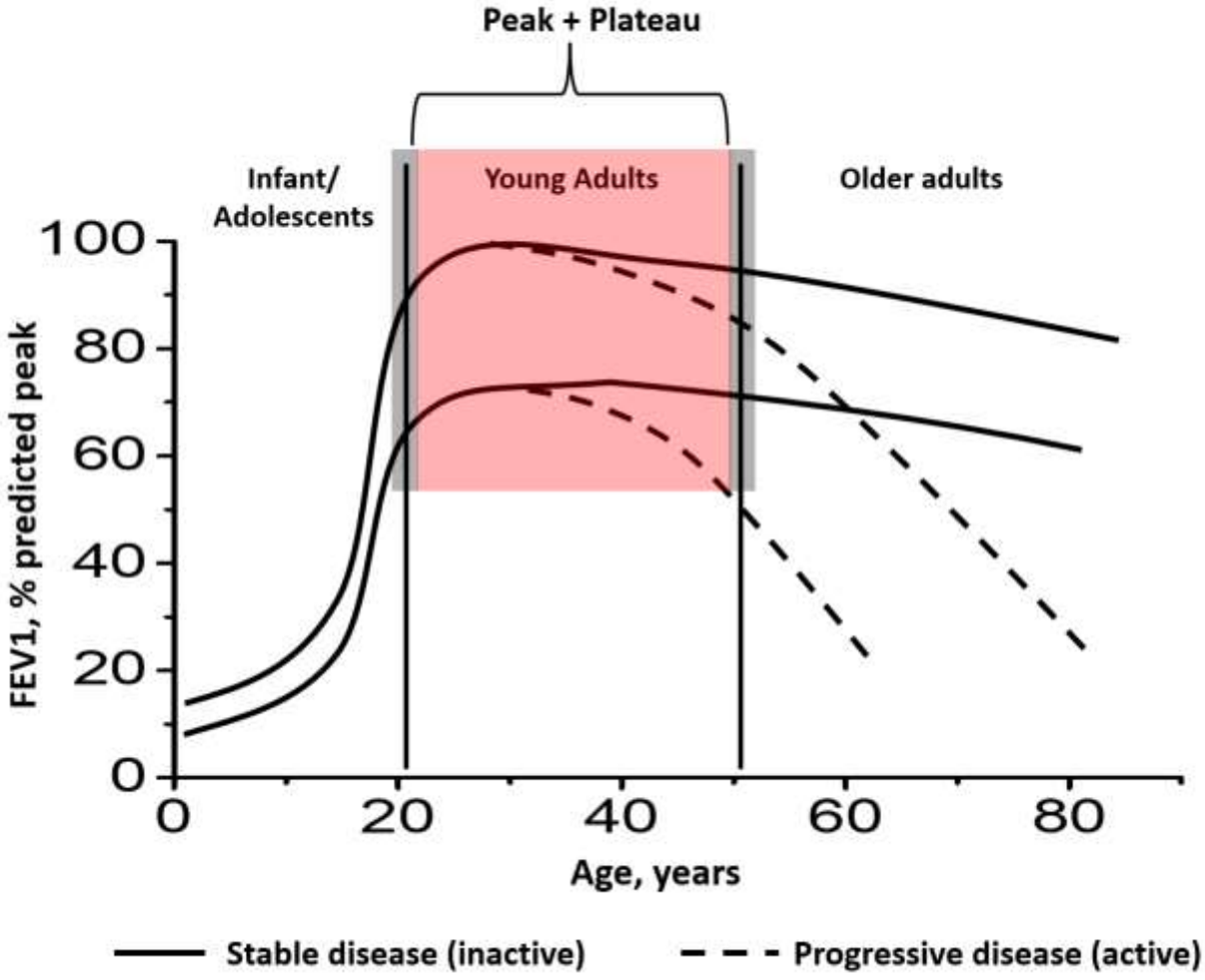
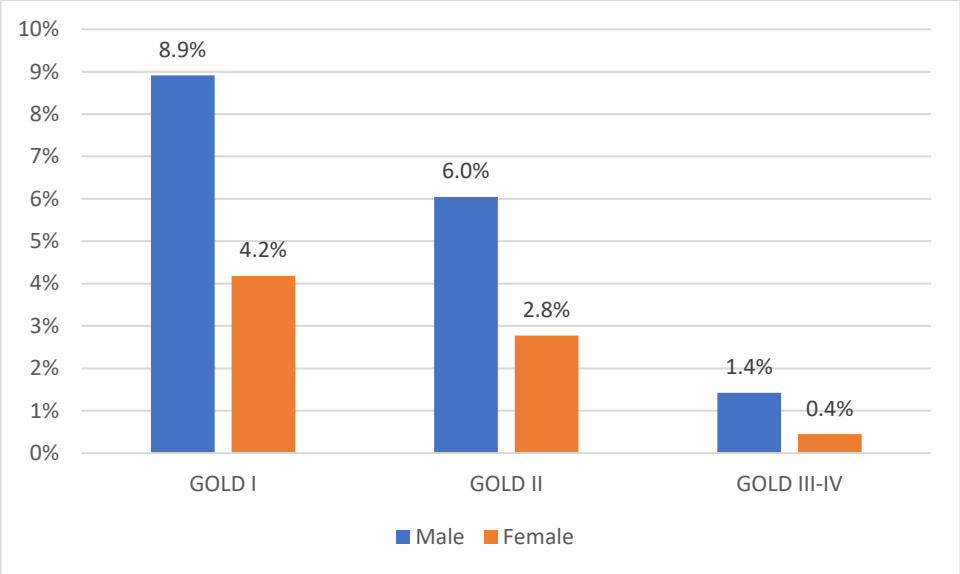


Figure 2. Prevalence of COPD in young individuals (20-49 years) in the general population in China. Data from (44).



1