



# What is asthma–COPD overlap syndrome? Towards a consensus definition from a round table discussion

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**ABSTRACT** Patients with asthma–chronic obstructive pulmonary disease overlap syndrome (ACOS) have been largely excluded from pivotal therapeutic trials and, as a result, its treatment remains poorly defined and lacking firm evidence. To date, there is no universally accepted definition of ACOS, which has made it difficult to understand its epidemiology or pathophysiology. Despite many uncertainties, there is emerging agreement that some of the key features of ACOS include persistent airflow limitation in symptomatic individuals 40 years of age and older, a well-documented history of asthma in childhood or early adulthood and a significant exposure history to cigarette or biomass smoke. In this perspective, we propose a case definition of ACOS that incorporates these key features in a parsimonious algorithm that may enable clinicians to better diagnose patients with ACOS and most importantly enable researchers to design therapeutic and clinical studies to elucidate its epidemiology and pathophysiology and to ascertain its optimal management strategies.



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**We propose that asthma–COPD overlap syndrome be defined based on three major criteria and one minor criterion** <http://ow.ly/3rOU304aTNm>

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## Introduction

A global expert panel discussion, comprising of specialists and generalists from North America, Western Europe and Asia, was held in Denver (CO, USA) on May 16, 2015, to discuss asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) and to develop a framework to scientifically and clinically advance the field. The experts discussed the current state of knowledge of ACOS and identified critical gaps in knowledge. These discussions were continued through electronic media (e.g. e-mail) until the end of February 2016 and any new relevant data that emerged in 2015–2016 were incorporated into these discussions. It should be noted that, while the group reached an agreement on the most salient features of ACOS through discussion, iteration and electronic communications, there was not uniformity or singularity of opinion. Moreover, we did not use a structured format (e.g. Delphi or nominal group method) to achieve consensus [1, 2]. Thus, in this paper, we use the word “consensus” synonymously with “agreement”, rather than the more technical definition, denoting convergence of opinions to singularity (or uniformity).

## The key consensus points of the discussions

1. For ACOS to move forward as a unique entity, a universally accepted operational definition is urgently required, even if it is not perfect. The panel favoured a definition consisting of major and minor criteria, analogous to the approach for operationally defining rheumatic fever [3].
2. The key features of ACOS, which should be considered in the operational definition, included: 1) persistent airflow limitation on spirometry despite adequate administration of a short-acting bronchodilator in subjects 40 years of age or older; 2) a “significant” history of cigarette smoking or an equivalent lifetime exposure to biomass; and 3) a physician diagnosis of asthma before 40 years of age.
3. While evidence-based treatments on ACOS are scarce, inhaled corticosteroids combined with a long-acting bronchodilator may be reasonable for ACOS patients, especially in those with elevated serum or sputum eosinophils. However, there is sufficient clinical equipoise to initiate clinical trials addressing this issue.

## Why is ACOS necessary as a “new” disease entity?

It has been long recognised that features of asthma and COPD may co-exist in patients who present with airflow limitation and symptoms of cough and/or dyspnoea [4]. Based on this observation, in 1961, Professor Orie stated that “bronchitis and asthma may be found in one patient at the same age but as a rule there is a fluent development from bronchitis in youth to a more asthmatic picture in adults, which in turn, develops into bronchitis of elderly patients” [5, 6]. Many years later, Fletcher coined the term the “Dutch Hypothesis” to describe the phenomenon of “asthma” becoming “COPD” [6]. Over the years, the merits of the “Dutch Hypothesis” have been hotly debated, with some arguing that asthma and COPD are unique conditions with separate and distinct pathophysiologies and treatments, while others suggesting a spectrum of disease, consistent with the “Dutch Hypothesis” [7].

In the face of this uncertainty, independent investigators and drug companies have traditionally made great efforts to exclude patients with overlapping features of asthma and COPD from pivotal registration clinical trials. Figures 1 and 2 summarise the inclusion and exclusion criteria of some recent phase III COPD and asthma trials. In almost all large COPD clinical trials, lifetime never smokers or those with a significant past or current history of asthma, allergic rhinitis or atopy (the latter two criteria because of their close association with asthma) have been excluded, though there have been some notable exceptions. In contrast, asthma clinical trials have almost always excluded patients with more than a 5 pack-year smoking history and many have also excluded current smokers. A key enrollment criterion for asthma clinical trials has been either 1) airway hyperresponsiveness or 2) significant bronchodilator reversibility (usually >12–15% improvement and/or 200 to 400 mL increase in forced expiratory volume in 1 s (FEV<sub>1</sub>) compared with pre-bronchodilator values). It should be noted, however, that >60% of patients with COPD with airflow limitation may also demonstrate airway hyperresponsiveness and/or significant bronchodilator reversibility [20, 21], though the mechanism for these features in COPD may be different than those in asthma [22].

Upon inspection of the inclusion and exclusion criteria of asthma and COPD clinical trials, it is apparent that modest smokers (<10 pack-years) with persistent airflow limitation and without a significant bronchodilator response have largely been excluded from both asthma and COPD therapeutic trials. The latter are predominantly women beyond 40 years of age, who may be very symptomatic from their airway disease and have a high burden of disease [23]. In the past, these patients have been called “asthmatics”, “asthmatic bronchitics”, or “chronic asthmatic bronchitics”, though most recently a diagnosis of COPD has been increasingly used [24–27]. Because of the traditional label of asthma in these patients, inhaled corticosteroids (with or without a long acting bronchodilator) are often prescribed and, in some cases, in very high doses, leading to adverse effects. However, supportive data for this approach are lacking.

	TORCH [8]	UPLIFT [9]	VOGELMEIER [10]	VERKINDRE [11]	TONNEL [12]
<b>Exclusion criteria</b>					
Diagnosis of asthma, non-COPD respiratory disorders					
History of asthma, allergic rhinitis or atopy					
Blood eosinophil count >600 cells- $\mu\text{L}^{-1}$					
<b>Inclusion criteria</b>					
Current or former smokers with $\geq 10$ pack-years					
Diagnosis of COPD with pre-BD FEV <sub>1</sub> $\leq 60\%$ predicted					
Post-BD (400 $\mu\text{g}$ albuterol) FEV <sub>1</sub> increased by <10%					
FEV <sub>1</sub> /FVC $\leq 70\%$					
Post-BD FEV <sub>1</sub> <70% predicted					
Residual volume >125% predicted					

Included in trials
  Not included in trials

FIGURE 1 Inclusion and exclusion criteria of select chronic obstructive pulmonary disease (COPD) therapeutic trials. BD: bronchodilator; FEV<sub>1</sub>: forced expiratory volume in 1 s; FVC: forced vital capacity.

Similarly, smokers with COPD who have had a prior or current history of asthma have also been largely excluded from pivotal therapeutic trials. Thus, while the use of inhaled corticosteroids is generally discouraged in patients with COPD, it is unclear whether patients with coexisting asthmatic features may benefit from a steroid-containing therapeutic regimen [28]. Indeed, this may explain why, in many countries around the world, inhaled steroid-containing inhalers are the most commonly prescribed medications in clinical practice for patients with COPD [29]. With the increasing concern about the cost and the potential adverse effects of inhaled corticosteroids in COPD, there is a pressing need to determine the role of inhaled corticosteroids in these patients.

Although the exact figures are hard to obtain and extremely variable (owing to major differences in the case definition of ACOS used across the studies), a recent report estimates that approximately 15% of adult patients with persistent airflow limitation may have significant overlap of COPD and asthma [30] and thus may have been excluded from therapeutic trials. Recent reviews have noted that ACOS is unlikely to be a single disease entity and is likely to be a collection of “diseases” with many different clinical phenotypes (e.g. presence of comorbidities), inflammatory biosignatures (e.g. T-helper (Th) type 2 *versus* Th1 inflammatory signatures in the airways) and disease pathogenesis [31, 32]. In view of this reality, some have suggested that the term “syndrome” be dropped (since syndrome implies a common pathogenesis) [33], while others have recommended that we move beyond diagnostic labels (which are often inaccurate and misleading) to focus on disease phenotypes and endotypes as a precondition for precision medicine [34, 35]. Others have advocated a major focus on “treatable traits” to promote optimal management of COPD patients with a variety of features (e.g. co-morbidities) that are modifiable with pharmacological and non-pharmacological interventions [36]. While these are reasonable tenets, we believe that before we entertain major changes in the nomenclature of disease entities, it is important to generate high-quality data to support any modifications that may occur. Moreover, it is important to note that these concepts are not necessarily contradictory and may even be complementary. It is possible (and perhaps desirable) to pursue a better understanding of ACOS, while at the same time providing good patient care by optimally treating the “treatable traits”.

	STEMPEL [13]	KERSTJENS [14]	PETERS [15]	AARONSON [16]	BUSSE [17]	HAAHTELA [18]	KUO [19]
<b>Exclusion criteria</b>							
Ever told by physician that they had chronic bronchitis, emphysema or COPD							
Current smoker							
Smoking >5 pack-years							
<b>Inclusion criteria</b>							
Clinical diagnosis of asthma ≥1 year prior to randomisation							
PEF ≥50% predicted							
FEV <sub>1</sub> >40% predicted							
Confirmed asthma diagnosis via either 1) 12% post-BD reversibility or 2) PC <sub>20</sub> <8 mg·mL <sup>-1</sup> not on ICS or <16 mg·mL <sup>-1</sup> on ICS							
Lifelong nonsmoker or smoking history of <10 pack-years and nonsmoker at enrolment							
≥15% FEV <sub>1</sub> reversibility with inhaled β <sub>2</sub> agonist							
≥15% FEV <sub>1</sub> decrease following an exercise test							
Histamine responsiveness <32 mg·mL <sup>-1</sup>							
Normal chest radiograph							

Included in trials
  Not included in trials

FIGURE 2 Inclusion and exclusion criteria in select asthma trials. COPD: chronic obstructive pulmonary disease; PEF: peak expiratory flow; FEV<sub>1</sub>: forced expiratory volume in 1 s; BD: bronchodilator; PC<sub>20</sub>: provocative concentration causing a 20% fall in FEV<sub>1</sub>; ICS: inhaled corticosteroid.

### How has ACOS been defined in clinical studies?

It should be noted that the operational definition of ACOS has varied across studies [37]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD)/ Global Initiative for Asthma (GINA) document on ACOS, for instance, advocates a “tick-box” approach to ACOS diagnosis consisting of certain clinical characteristics (e.g. doctor diagnosis of asthma and exposure to noxious stimuli) and spirometric features (e.g. a “significant” bronchodilator response) [38]. However, it is unclear how many (or which) “tick” boxes need to be checked off before ACOS can be diagnosed. Others have suggested, in addition to a combined history of asthma and COPD, objective measures such as a “large” bronchodilator response on FEV<sub>1</sub>, serum IgE levels or eosinophil counts on sputum [39, 40].

Although there is heterogeneity, most guidelines and publications largely agree on the following components or traits of ACOS: 1) presence of persistent airflow limitation in adults 40 years of age and older; 2) a significant smoking or biomass exposure history; and 3) a history of atopy or asthma [40].

#### Persistent airflow limitation

GOLD has defined persistent airflow limitation based on a fixed cutoff of post-bronchodilator FEV<sub>1</sub>/forced vital capacity (FVC) <0.70 [41]. While this is most commonly used due to its simplicity, there is a compelling argument for using age-adjusted cutoff values. The more controversial aspect of ACOS is the bronchodilator response. The American Thoracic Society (ATS) criterion for a significant bronchodilator

response is an FEV<sub>1</sub> or FVC improvement of  $\geq 200$  mL or 12% from baseline values [42]. However, this threshold cannot reasonably separate asthma from COPD. Indeed, one study reported a receiver operating characteristics area under the curve (ROC–AUC) value of 0.57 regardless of whether FEV<sub>1</sub> or FVC thresholds were used [43]. To improve the diagnostic performance, the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) has recommended the use of 15% and 400 mL as the cutoff for patients with only one spirometric measurement or the traditional 12% and 200 mL cutoff for those with multiple measurements [38]. Similarly, the GOLD/GINA document recommends the use of 15% and a 400 mL cutoff for ACOS. However, none of these cutoff values has been shown to have excellent performance characteristics in clearly separating asthma and COPD. Moreover, bronchodilator response (BDR) in general is highly variable over time in COPD [44]. Thus, the usefulness of BDR for diagnosing ACOS is uncertain.

#### *Recommendations on the spirometric criteria for ACOS*

Persistent airflow limitation should be a major criterion for ACOS. Thus, it is imperative to perform pre- and post-bronchodilator spirometry according to ATS/European Respiratory Society (ERS) recommendations in all patients. An age-adjusted cutoff value for FEV<sub>1</sub>/FVC is preferred; however, in some jurisdictions where normative values are not widely available, fixed ratio cutoffs can be used. It is preferred that this criterion be met with multiple (and not just a single) spirometric measurements over time.

While significant BDRs have been traditionally linked with asthma, it is now well known that some patients with COPD demonstrate significant improvements in FEV<sub>1</sub> following bronchodilators. However, in general, the BDRs tend to be small in magnitude and quite variable in patients with COPD [45], unlike in asthma where BDRs are generally larger and more robust. The committee believes that given the uncertainty of BDR thresholds in separating patients with COPD *versus* those with asthma, it should not be a major criterion for ACOS with the following exception.

In individuals who do not have a physician diagnosis of asthma before the age of 40 years, BDR may be used as a major diagnostic criterion of ACOS if the subject demonstrates a very large BDR, defined as  $>400$  mL [46] increase in baseline FEV<sub>1</sub> following 400  $\mu$ g of albuterol/salbutamol (or equivalent). This exception is being permitted as some individuals may manifest their first symptoms of asthma at age 40 years or older [47].

#### *Tobacco smoking and biomass exposure*

Although the pathogenesis of COPD is not entirely known, it is well established that in most high-income countries, cigarette smoking is the leading environmental risk factor accounting for 60–80% of the cases [48, 49]. Despite the worldwide efforts to curb the use of cigarettes, smoking is common in most countries [50]. Even in the USA and Canada, where anti-smoking policies and legislation are very stringent, the prevalence of smoking is 15–20% among adults 20 years of age and older. Counter-intuitively, in most countries, the prevalence of smoking in adult asthmatics is similar to the general population without asthma [51]. Epidemiological studies suggest that asthma and cigarette smoking synergistically accelerate the rate of decline in lung function in adults [52]. Female smokers in particular may be at increased risk of COPD [48]. Thus in women, COPD may develop with only a modest number of pack-years of smoking and the traditional cut-offs of 10 pack-years may be too stringent. In developing countries, cigarette smoking is also an important driver of COPD; however, biomass exposure may also play a significant role in the pathogenesis of COPD, especially among women [48, 53]. Indeed, in developing countries, the population-attributable risk of COPD for indoor air pollution, mostly in the form of biomass smoke, is 26% (similar to that imposed by tobacco smoking, also at 26%) [49]. Interestingly, biomass-related COPD may have a different phenotype (airway predominant) and disease pathogenesis compared with tobacco-related COPD (which is a variable mix of emphysema and airway disease) [54, 55]. Despite the growing burden of biomass-related COPD (non-tobacco related COPD), no large-scale therapeutic trials have been conducted in this population of patients. Thus, evidence-based therapeutic choices for these patients are completely lacking.

#### *Recommendation on the environmental exposure for ACOS*

Current or past cigarette smoking should be a major criterion for ACOS. However, there is uncertainty on the exact pack-year cutoff that is appropriate for ACOS. Until more data are available, a reasonable cutoff is  $\geq 10$  pack-years for smokers in countries where biomass exposure is not a major contributor to airflow limitation (e.g. North America and Western Europe).

It should also be noted that in some parts of the world (e.g. Africa, Southeast Asia and China), indoor and outdoor pollution play a key pathogenic role in asthma and COPD in non-smokers or intermittent (light) smokers. However, there is no universally accepted method to quantitate these exposures. Thus, in these jurisdictions, the committee recommends that this criterion may be fulfilled in non-smokers or smokers with  $<10$  pack-years, who have “equivalent” biomass or outdoor air pollution exposure as deemed by their primary healthcare provider.

### *History of asthma or atopy before age 40 years*

Childhood asthma is common, affecting ~10% of the population in industrialised countries. However, many children (~80%) “outgrow” their asthma when they reach adulthood [56]. Clinical features that are predictive of remission include lack of sensitisation and allergen exposure, higher baseline FEV<sub>1</sub> and reduced airway hyperresponsiveness at the first assessment [57]. Asthma can also develop in “adulthood” (arbitrarily defined as asthma onset after 12 years of age [58]). Adult-onset asthma often occurs in non-atopic females with a history of rhinitis [59]. It is often fraught with a large burden of symptoms [60] and is associated with persistent airflow limitation and accelerated decline in lung function [60, 61]. It should be noted, however, that while both rhinitis (especially allergic rhinitis) and atopy are significant risk factors for asthma, elevating the risk of asthma by 1.67- and 3.90-fold, respectively [62], fewer than 50% of the adults with these features (followed for more than 8 years) develop asthma [62]. Interestingly, a recent study of ACOS suggested that COPD patients with a history of asthma may have different clinical features compared with COPD patients without a history of asthma including a significant BDR, higher eosinophil counts in the blood, and elevated total serum IgE concentrations [63].

### *Recommendation on history of asthma or atopy before age 40 years*

A history of childhood or adult-onset asthma should be a major criterion for ACOS. As the prevalence of COPD increases after age 40 years, an age cutoff of 40 years is reasonable to improve the accuracy of the diagnosis.

However, the committee also recognised that asthma can develop in individuals 40 years of age and older. Although COPD patients can demonstrate a significant BDR, it is generally less than 400 mL [45]. Thus, in those without a documented history of asthma before 40 years of age, this criterion may be met by demonstrating a BDR of >400 mL [46] (please see previous discussion on this).

While many patients with asthma have a history of atopy and/or rhinitis, a substantial proportion of adults with atopy and rhinitis do not have or develop asthma [62]. Thus, a history of atopy and rhinitis should not be a major criterion for ACOS.

### *Blood or sputum eosinophil count and other biomarkers*

In one study, patients with established COPD, who also had a history of asthma or “asthmatic” symptoms (episodic breathlessness, wheezing, cough and chest tightness worsening at night or in the early morning) [64] had on average a two-fold increase in serum IgE levels and peripheral eosinophil count and a six-fold increase in sputum eosinophils (as a % of total cell count). Interestingly, the COPD patients with asthma, in that study, were more likely to be responsive to inhaled corticosteroids than COPD patients without asthma [64]. Other studies have evaluated the potential usefulness of fractional exhaled nitric oxide (FeNO) and parameters on computed tomography (CT) (e.g. airway wall thickness) to distinguish ACOS from COPD [65]. While these features are useful for research purposes, clinical application has been more challenging owing to, in certain cases, poor standardisation of measurements across centres (e.g. sputum eosinophilia and CT assessments) and lack of clinically defined thresholds to define ACOS. For example, using the upper limit of normative values, approximately 1 in 3 patients with COPD has elevated serum IgE levels (>100 IU·mL<sup>-1</sup>) [65]; however, it is not entirely clear whether this threshold has any clinical relevance for patients with COPD. Measurement of blood eosinophils, unlike sputum eosinophil counts, is a well-standardised and reproducible test in most clinical laboratories. Although, on average, COPD patients with asthmatic features have elevated peripheral eosinophils, there is little agreement on what constitutes the most appropriate cutoff values. Some have suggested a cutoff of 5% [30], while others have advocated a 2% cutoff [66] and still others have suggested using an absolute cell count cutoff (e.g. 300 cells·uL<sup>-1</sup>) [67] with no consensus on what the absolute threshold should be. Similar problems plague measurements of FeNO. There is no well-established cutoff value that defines an “asthmatic” phenotype among smokers with airflow limitation. Some have suggested a cutoff value of 35 parts per billion (ppb) [65], while others have recommended a 50 ppb threshold [38]. Given the paucity of data on FeNO in ACOS, a firm recommendation is not possible.

### *Recommendation on biomarkers of asthma*

There is a pressing need for an objective biomarker of ACOS; however, to date, there is no consensus on what that biomarker should be. The most promising is peripheral eosinophil count owing to the ease of measurement and the standardisation of the assay that enables within and across patient and centre comparisons. It may also relate to important clinical outcomes such as risk of exacerbations [68] and therapeutic responsiveness to inhaled corticosteroids [69]. However, currently, there is no agreement on what constitutes the optimal cutoff value for defining ACOS. The most commonly reported value in the literature is 2% [66, 69–71]; however, there have been many other cutoff values that have been reported [72]. The committee generally felt that the 2% threshold lacked sufficient specificity to diagnose eosinophilic airway inflammation [73]. Until more evidence is available, the committee endorses a higher threshold of blood



eosinophils (e.g.  $\geq 300 \cdot \text{uL}^{-1}$ ) to increase the specificity of the biomarker to diagnose eosinophilic airway inflammation as a minor criterion for ACOS.

The other biomarkers discussed in this section lack sufficient strength of evidence for consideration in either the major or minor criterion for ACOS. Serum IgE titres are the most promising among this group owing to its availability and standardisation. However, the cutoff values have not been well defined and as such serum IgE measurements cannot be recommended at this time for inclusion in the ACOS definition.

### **Responsiveness to inhaled corticosteroids**

There is a general feeling that patients with ACOS compared with patients with COPD are more responsive to inhaled corticosteroids. However, strong evidence is not available to support this notion. In one study, PARK *et al.* [74] evaluated FEV<sub>1</sub> improvement after 3 months of treatment with a fixed-dose inhaled corticosteroid/long-acting  $\beta_2$  combination (ICS/LABA). They found that patients with “ACOS” features (defined as COPD plus elevated peripheral eosinophils) were twice as likely than patients with COPD to have a significant therapeutic response (defined as a  $\geq 12\%$  and  $\geq 200$  mL improvement in FEV<sub>1</sub> above baseline at 3 months) to ICS/LABA. These results require validation and refinement before they can be adopted into clinical practice for patients with ACOS. For instance, it is not entirely clear that a 3 month improvement in FEV<sub>1</sub> with ICS/LABA will translate into improvements in patient-oriented or long-term outcomes and, in future studies, it may be more appropriate to evaluate ICS alone (without LABA) to clearly understand the impact of ICS therapy on ACOS patients.

### **Recommendation on ICS responsiveness in ACOS**

Given that ICS is highly effective in most patients with asthma [75], it is tempting to believe that patients with ACOS would experience benefits from ICS. However, there are very few studies, if any, that have validated this notion. Until a consensus can be reached on the definition of ACOS, it may not be possible to conduct trials to address this critical question. ICS-responsiveness by itself cannot be included in the definition of ACOS as it would constitute a “self-fulfilling” prophecy. Thus, the committee does not endorse its inclusion in the ACOS definition either as a major or minor criterion.

### **Recommendations on a case definition of ACOS**

Table 1 summarises the major and minor criteria that the committee recommends be used in the diagnosis of ACOS. The committee believes that patients who meet all three major criteria and at least one minor criterion be considered for the diagnosis of ACOS.

The committee recognises that this is an arbitrary definition and one that requires careful validation. Accordingly, these criteria are dynamic and with the addition of new data, modifications may be required.

Notwithstanding the limitation of this approach, for the field to move forward, a consensus definition, even an imperfect one, is urgently required. Without such a case definition, it is impossible to collect (let alone interpret) data on its epidemiology, clinical course or therapeutic responsiveness. This lack of consensus, for instance, may explain the widely divergent data on the prevalence of ACOS, which ranges between 11% to 56% among patients previously diagnosed with COPD [35], 13% to 61% among patients previously diagnosed with asthma [76] and  $\sim 2\%$  in the general population over 40 years of age [77]. It may also explain why in some studies, ACOS has been associated with more female patients [78, 79], while in others with more male patients [30, 80]. ACOS has been associated with increased risk of poor quality

TABLE 1 Criteria for diagnosis of asthma–chronic obstructive pulmonary disease overlap syndrome

Major	Minor
1. Persistent airflow limitation (post-bronchodilator FEV <sub>1</sub> /FVC <0.70 or LLN) in individuals 40 years of age or older; LLN is preferred	1. Documented history of atopy or allergic rhinitis
2. At least 10 pack-years of tobacco smoking OR equivalent indoor or outdoor air pollution exposure (e.g. biomass)	2. BDR of FEV <sub>1</sub> $\geq 200$ mL and 12% from baseline values on 2 or more visits
3. Documented history of asthma before 40 years of age OR BDR of >400 mL in FEV <sub>1</sub>	3. Peripheral blood eosinophil count of $\geq 300 \text{ cells} \cdot \text{uL}^{-1}$

The committee recommends presence of all three major criteria and at least one minor criterion for asthma-chronic obstructive pulmonary disease overlap syndrome. FEV<sub>1</sub>: forced expiratory volume in 1 s; FVC: forced vital capacity; BDR: bronchodilator response using 400 ug of albuterol/salbutamol (or equivalent); LLN: lower limit of normal.

of life and hospitalisations [81, 82], though paradoxically with reduced rates of lung function decline compared with COPD alone [81]. Until a case definition is determined, these epidemiological and clinical data will be hard to interpret and across study comparisons will be impeded.

### Future directions of ACOS: unresolved issues that require urgent attention

As noted previously, a consensus definition is urgently needed and the first critical enabling step in understanding the clinical context of this entity, measuring the size of the problem by reanalysing both population data and unbiased clinical series of respiratory patients [83], and designing therapeutic and biomarker trials.

Once a definition is established, large longitudinal (non-interventional) studies, or retrospective observational studies are required to understand the clinical and natural history of this entity.

There is also a pressing need to understand the molecular mechanisms of ACOS and its related phenotypes. A recent study suggests that patients with COPD who have clinical features of asthma have an enriched bio-signature of Th2 processes in the airways similar to what is found in the “typical” asthmatic airway (and in contrast to Th1 bias in the “typical” COPD airway) [84]. Another study suggests that there may be different genetic drivers in ACOS than in typical COPD or in asthma [85]. Large and more robust longitudinal data are required to validate these early findings and to discover novel molecular pathways involved in ACOS.

There is also an urgent need to understand the role of inhaled corticosteroids in ACOS. It is widely presumed (but not proven) that patients with ACOS will derive therapeutic benefits from ICS [86]. However, prospective clinical trials are required to validate (or refute) this notion and establish the cost-effectiveness of this approach.

There is also a pressing need to develop easily accessible biomarkers of ACOS. Reliance on a patient’s history of “asthma” may be unreliable, leading to misclassification bias. BDR threshold of 400 mL in FEV<sub>1</sub>, while intuitive, lacks solid data supporting its use in ACOS. Blood eosinophil counts and serum IgE concentrations are promising but require additional validation before their clinical use can be advocated.

ACOS may not be a single entity. There may be different endotypes within ACOS. For example, it is not certain whether asthmatics who develop fixed airflow limitation related to ageing and/or environmental exposure (smoking or biomass) will have the same molecular drivers, therapeutic responsiveness and prognosis as patients with COPD who have certain “asthmatic” features. Additional work will be needed to elucidate endotypes of ACOS.

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