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Definitions and Diagnosis of COPD: State of the Art

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With high prevalence and high burden, the condition we call 'chronic obstructive pulmonary disease' (COPD) is not so much a respiratory concern as a public-health epidemic (1). This is particularly true in low- and middle-income countries (LMICs) where most cases remain undiagnosed and untreated. With recent changes to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition of COPD (2), and publication of the Lancet Commission on COPD (1), we review current state-of-the-art in relation to COPD definition and diagnosis, and why remaining inconsistencies matter.

Defining and Classifying COPD

GOLD have recently updated their definition of COPD as '*a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnoea, cough, sputum production) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction'* (2). However, persistent airflow obstruction can be caused by factors other than tobacco-smoke exposure, which is the most frequent cause in high-income settings, and not all such causes are associated with the airway inflammation that has been considered a hallmark of COPD. Such factors include those which impede lung growth in early life, asthma, and the consequences of infections such as post-TB lung damage and bronchiectasis (3,4). These differing pathologies have now been highlighted by GOLD as 'etiotypes' in a newly-proposed taxonomy for COPD (2).

'Etiotyping' has little current impact on COPD management as, with the specific exception of alpha-1 antitrypsin deficiency (A1ATD) as an exemplar of genetically-determined COPD, management does not differ between etiotypes. In part, this is because clinical trials have focused on tobacco-smoke driven COPD, such that the evidence base to treat persistent airflow obstruction from other causes is, in general, absent and this remains an unmet need. The Lancet Commission's proposed five types of COPD are broadly consistent with GOLD's etiotypes, but use different terminology. In addition to

the difference in terminology, the GOLD classification includes categories for COPD associated with asthma, and 'idiopathic' COPD (Table 1).

TABLE 1: COPD 'etiotypes' in GOLD and Lancet Commission

GOLD 2023	Lancet Commission
COPD-G: Genetically Determined	TYPE1: Genetically Determined
COPD-D: Abnormal Lung Development	TYPE 2: Early Life Events
COPD-I: Infections	TYPE 3: Infection Related
COPD-C: Cigarette Smoking (and vaping)	TYPE 4: Smoking or Vaping
COPD-P: Biomass and Pollution Exposure	TYPE 5: Environmental Exposure
COPD-A: COPD and Asthma	
COPD U: Unknown cause.	

We suggest that caution must be given to some of these COPD 'etiotypes' as the pathologies underpinning them, for example impaired lung growth and development, likely do not represent the ongoing inflammatory lung disease that is usually considered to characterise COPD (5). We argue that such conditions are not COPD, in the sense of a genetically susceptible lung being exposed to sufficient airborne environmental stimuli and inducing inflammatory airway and alveolar change. Thus, labelling such conditions as 'COPD' risks over-treatment. Furthermore, some individuals will have multiple etiotypes. Indeed, one could argue that all COPD is 'genetically determined' to a greater or lesser extent.

Nevertheless, there are some advantages to etiotyping. It may raise awareness amongst the wider medical community (not only those working in respiratory medicine) that persistent airflow obstruction can be caused by factors other than tobacco smoking. Etiotyping may also lead to clinical trials focussing on specific populations of COPD patients, such as those with COPD related to biomass exposure, which may lead to more personalised management.

Thus, we argue that there is a place for etiotyping in COPD classification, with the acknowledgment that some patients may belong to multiple etiotypes, and a more unified approach to etiotyping is needed (considering the differences between GOLD and the Lancet Commission).

Diagnosing COPD

Whilst the GOLD definition of COPD is broad, there is a disconnect between the definition and the diagnostic criteria which specifically require the presence of post-bronchodilator (fixed) airflow obstruction (FAO). We have already argued that some causes of FAO are likely to have very different pathology from the inflammatory condition that GOLD has classically considered to be COPD. Conversely, whilst emphysema without FAO does not meet diagnostic criteria for COPD it is mentioned in the definition. We propose that broader diagnostic criteria for COPD are needed to align with the more inclusive GOLD definition of COPD, and to better reflect the spectrum of exposure-related 'COPD'. This sentiment is shared by the Lancet Commission, who do not offer an alternative definition of COPD but do state that COPD can be diagnosed using alternative lung function tests or CT of the lungs, and thus FAO should not be a mandatory diagnostic criterion (1). Figure 1 shows a proposed algorithm for COPD in which the diagnostic criteria and definition are consistent, based on the concept of COPD as an inflammatory condition of the lung that occurs when a genetically susceptible individual is exposed to sufficient airborne environmental stimulus.

Whilst fixed airflow obstruction, defined as a post-bronchodilator forced expiratory volume in one second (FEV1)/ vital capacity (VC) ratio <0.7, has been used by GOLD as a mandatory diagnostic criterion for COPD for decades (6), this approach has several further limitations. People with clinically significant disease are often diagnosed late, when irreversible damage has already occurred. By the time airflow obstruction defined as above is detectable, patients have lost 40% of their terminal bronchioles (7). Conversely, nearly 50% of smokers without airflow obstruction demonstrate emphysema on CT imaging, associated with increased symptoms and risk of future FAO compared to smokers without emphysema (8). 50% of smokers without airflow obstruction have daily respiratory symptoms, and this group are three times more likely to experience a respiratory infection than asymptomatic smokers (9). The disconnect between the more inclusive GOLD definition of COPD and its diagnostic criteria may prevent people with 'pure' emphysema from accessing appropriate 'COPD' care. A further example of problems arising from requiring FAO to diagnose COPD is for people with combined pulmonary fibrosis and emphysema (CPFE), who can have disabling symptoms yet apparently 'normal' spirometry (10). The absolute requirement for airflow obstruction to diagnose COPD has also restricted research and thus the therapeutic evidence base, and this is particularly true for early disease where the need for novel treatments is greatest. This has led to GOLD developing the concept of 'Pre COPD'.

'Pre-COPD' is controversial, in part because not all people so classified will progress to COPD. Pre-COPD in GOLD encompasses those without FAO, but who do have respiratory symptoms and/or 'other detectable structural and/or functional abnormalities' (2). GOLD separates out those with restrictive spirometry or 'preserved ratio impaired spirometry (PRISm)'. Both groups are heterogeneous, including some with changes that will progress to COPD, and others with very different pathology and phenotypes. The Lancet Commission approach has been to broaden diagnostic criteria to include those with 'Pre-COPD' pathology who are likely to progress to COPD as COPD.

Clearly, the entity known as 'COPD' lies on a spectrum of airborne exposure-related conditions. This spectrum may include those with 'Pre-COPD' (11). Given that people with 'Pre-COPD' may experience daily respiratory symptoms, the application of this new term may mean that more attention is given to these individuals and their symptoms. This could lead to more effective strategies for primary prevention of COPD, such as smoking cessation.

How to manage those with 'PRISm', defined as a preserved FEV1/VC ratio but FEV1 <80% predicted/below the lower limit of normal (2,12) is more difficult given that this pattern of abnormality need not relate to aetiologies that drive COPD, being commonly seen in those with higher body mass index and interstitial lung diseases for example, and PRISm may not be stable over time (13). A major challenge is that clinical trials have, in general, restricted recruitment to those meeting the traditional GOLD spirometric definition of airflow obstruction, and ignored important groups including, but not limited to chronic bronchitis, 'PRISm' and emphysema. Importantly, recent evidence has shown that dual-bronchodilators do not improve respiratory symptoms in current and former smokers without airflow obstruction (14), emphasising the importance of addressing the research gap in these other groups.

A further problem with FAO remaining a mandatory diagnostic criterion for COPD is sensitivity. Hand-held spirometers reliably diagnose airflow obstruction and so may be useful in primary care settings (15), although access to and expertise in spirometry has remained very variable despite this being the fundamental test to diagnose such a prevalent condition. Peak flow monitoring has reasonable concordance with spirometry in detecting airflow obstruction, and can be used with COPD questionnaires for COPD case-finding, which may be particularly relevant in LMICs (16,17). Ideally, case-finding tools should be used to identify those most at risk and therefore most in need of scare spirometry, but the World Health Organisation (WHO) have stated that, in the absence of

spirometry, lack of a post-bronchodilator improvement in peak expiratory flow rate means that a COPD diagnosis is “likely” when there are clinical features suggestive of COPD (18). Mid-expiratory flows (MEF), whilst less reproducible than FEV1 and VC, can be used to infer small airways disease (19), and reductions of MEF have been identified in people with Pre-COPD (20), and predict FEV1 decline in people with A1ATD who have not yet developed COPD as defined by GOLD (21). A focus on FEV1, a poor surrogate outcome measure, has distorted and delayed progression to new interventions in COPD.

If spirometry does not show post-bronchodilator airflow limitation, then other tests may be used to identify people who likely have COPD. Measuring lung volumes may show evidence of hyperinflation, a characteristic feature of COPD and emphysema (22), and indicate the potential for benefit from volume reduction interventions. Measures of gas transfers, such as diffusion capacity for carbon monoxide (DLCO), predict all-cause mortality in COPD (23) and is a better physiological assessment of emphysema. Impulse oscillometry measures airflow resistance at tidal breathing, giving an advantage over effort-dependent spirometry, and may be a more sensitive marker of early small airway disease than spirometry (24,25). Multiple breath washout is a technique used to measure lung clearance index, which can identify ventilatory heterogeneity (a feature of early COPD) (26,27). Lung clearance index is repeatable and associated with impaired FEV1 and COPD hospitalisations (28,29). In the Lancet Commission’s diagnostic algorithm, COPD can be diagnosed if one or more of these alternate lung function tests are abnormal. Many of these tests, especially those more recently developed (such as impulse oscillometry and lung clearance index) lack internationally agreed cut-offs for obstructive airways disease. Therefore, making a definitive diagnosis of COPD based on these tests may be challenging for practising clinicians.

CT chest is a diagnostic test with increasing importance in the assessment of COPD, and its use is becoming widespread (especially in higher-income countries). COPD features visible on CT chest, such as emphysema and air trapping, correlate with symptoms, disease progression and exacerbation risk (30). The Lancet Commission state that COPD can be diagnosed based on CT findings, and this would be consistent with the GOLD definition (but not diagnostic criteria, which would consider this Pre-COPD in the absence of airflow obstruction). However, some of these CT chest features are not found exclusively in COPD (31).

CT also has an important role once a COPD diagnosis has been made. It can identify important co-morbidities (such as bronchiectasis and coronary artery disease), which may not yet have been

diagnosed and are independently associated with all-cause mortality (32). It may raise the suspicion of A1ATD where there is basal-predominant emphysema. CT may also demonstrate lung nodules, including cancer, and emphysema on CT is associated with lung cancer mortality, which further highlights the importance of CT in the diagnostic work-up of COPD as emphysema cannot be diagnosed using spirometry (33). CT is essential to assess eligibility for lung volume reduction interventions (34). Conversely, the increasingly widespread use of CT for lung cancer screening offers opportunities to case-find previously undiagnosed COPD, by reporting emphysema as an 'incidental' finding (35).

There is increasing recognition that A1ATD is underdiagnosed (36,37), and so there is an argument for screening all COPD patients in areas of higher prevalence (as advocated by the WHO over 25 years ago) (38). The PiZZ genotype occurs in 0.08-0.24% of European COPD patients (39). A1AT testing should be considered in COPD patients less than 50 years old or with characteristic pan-lobular emphysema (40), primarily to guide assessment of liver disease in the index case, enable consideration of family screening, and to assess for augmentation therapy where this is available.

Additional diagnostic investigations can help refine the phenotypes and 'etiotypes' of COPD and inform on treatment response ('treatable traits'). The blood eosinophil count informs the current pharmacological treatment algorithm for COPD, based on evidence that higher counts predict better response to inhaled corticosteroid therapy (41–43). The full blood count is also useful in informing on anaemia as a differential cause of breathlessness, and polycythaemia suggesting chronic hypoxaemia.

There are several emerging COPD diagnostic tests which may reach clinical practice in the future. Parametric response mapping (a voxel-based technique which uses CT chest images) can infer the presence of small airways disease (44,45). Artificial intelligence will likely become increasingly important in COPD diagnostics. For example, deep learning algorithms may be used to assess the severity and phenotype of COPD based on CT lung images (46), and to assist in interpretation and quality-assurance of spirometry (47,48). Changes in the lung microbiome occur with different COPD severities, and between frequent and infrequent exacerbators (49,50) but, for now, remain a research tool. Future diagnosis and stratification might mirror the approach of lung cancer, in which analysis of endobronchial biopsy is made to define genetic mutations and guide treatment.

The Importance of a Timely Diagnosis

The inconsistencies between definition and diagnosis, and complexities including the heterogeneity of diseases, mean that people with 'COPD' are often not diagnosed in a timely way. Timely diagnosis is a key component of the recent COPD patient charter (51). Delayed diagnosis means accumulation of irreversible lung damage. For the moment, only exposure reduction has been proven to reduce the risk of disease progression in early disease, nevertheless this is a target for future opportunity and disease-modifying therapies. The natural history of other chronic inflammatory conditions, such as inflammatory arthritis and inflammatory bowel diseases, has been transformed by the early initiation of disease-modifying interventions prior to the accumulation of irreversible organ damage. The reasons why specific interventions (such as anti-TNF) have not been effective, and indeed may be harmful in COPD (52) are not well understood and likely complex, including initiation when there is established end-organ damage, in the context of an altered microbiome and where there is increased co-morbidity and cancer risk.

Delayed initiation of therapy also means ongoing symptoms, increased risk of exacerbations, and increased risk of developing co-morbidity, notably cardiovascular disease. Delayed diagnosis leading to delayed optimisation of care is therefore also likely to lead to increased overall health-care costs (53). Initiation of effective therapy is particularly challenging in LMIC settings where access to affordable medicines (54), and challenges in the implementation of guidelines (55), even where these exist (56,57), are major barriers to care.

CONCLUSION

There is an absence of evidence for the treatment of COPD related to exposures other than tobacco smoking. Recent changes to the classification of COPD bring much-needed attention to these other exposures. We hope this leads to trials featuring specific COPD populations, however, personalised treatment may still not be effective if the diagnosis is made too late. Thus, approaches to align diagnostic criteria with the definition of COPD are needed, as is the recognition of 'Pre-COPD'. To achieve the revolution required to address COPD will require these fundamental issues to be addressed, and for the community to move forwards together. We must rise to that challenge.

FIGURE LEGEND:

Figure 1: Definitions and diagnosis of COPD, Pre-COPD and alternative causes of airflow obstruction.

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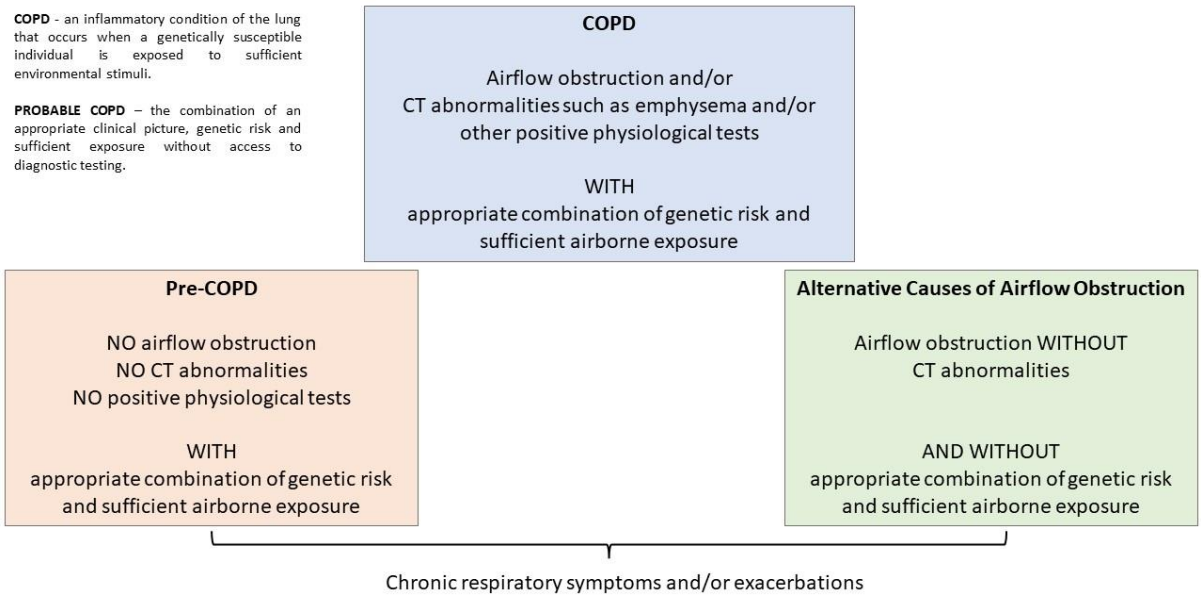

Figure 1: Definitions and diagnosis of COPD, Pre-COPD and alternative causes of airflow obstruction.