One-Off Spirometry is Insufficient to Rule-In or Rule-Out mild-moderate COPD

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Making an accurate diagnosis of COPD matters. For those affected, it is the initial step in accessing appropriate interventions. First and foremost, this should start by minimising future inhaled exposures. Similarly, for those not affected, excluding COPD avoids unnecessary prescription of drugs that would have no benefit, are costly and may have side effects, and can prompt a search for alternative diagnoses. Everyone, wherever they live in the world, deserves access to an accurate COPD diagnosis.

So far so good, but it turns out making an accurate diagnosis of COPD is not straight forward. Firstly, COPD exists as part of a spectrum of lung disease arising when a genetically susceptible individual is exposed to sufficient inhaled environmental toxin. Large airway involvement is characterised by cough and sputum leading to the *clinical* diagnosis of chronic bronchitis. Destructive alveolar involvement results in the anatomical, and thus *radiological* diagnosis of emphysema. COPD is a physiological diagnosis defined by, and therefore diagnosed when, there is poorly-reversible airflow obstruction. This must be in the presence of exposure to sufficient, recognised toxin, typically cigarette or biomass smoke, or increased susceptibility to such toxin, as in alpha-1 antitrypsin deficiency. The airflow obstruction results from mucus plugging and loss of alveolar attachments, but also intrinsic involvement of the small airways with inflammation and fibrosis in the wall [1]. Of note, there are other causes of poorly reversible airflow obstruction besides COPD, for example chronic asthma and bronchiectasis. Not everyone with poorly-reversible airflow obstruction has COPD.

Poorly-reversible airflow obstruction is defined by a reduced post-bronchodilator ratio of Forced Expiratory Volume in 1 second (FEV_1) to (Forced) Vital Capacity (F)VC. Even here, the picture is complex. This is not the platform to rehearse arguments for and against the approach of defining COPD using a fixed FEV_1/(F)VC ratio <0.70, or defining abnormality using the lower limit of normal (LLN; <5th percentile) [2]. Note that both approaches, by necessity, have a hard threshold defining normal from abnormal. Whichever approach is used, an unanswered problem has been how to handle those people with a ratio at the boundary of normal? This issue of the *Journal* features an important paper that examines this question, and therefore informs on diagnostic uncertainty in COPD.

Aaron and colleagues [3] provide an analysis of 'diagnostic instability' in COPD, defined as crossing and re-crossing the diagnostic FEV_1/(F)VC threshold. The study also examined 'diagnostic reversals', defined as subjects meeting criteria for COPD at study onset, then normalising and remaining normal over the subsequent period of observation. A total of 7,412 patients were studied across two established cohorts over 4-5 years. The bottom line is a significant risk of diagnostic instability, particularly (and predictably) greatest for those patients closest to the threshold. The instability rate was 19.5% in the Lung Health Study (LHS) cohort and 6.4% in the CanCOLD cohort. There were differences between the cohorts in the number of visits, and in smoking status, both of which likely contributed to the observed differences in diagnostic instability rate. The instability rate estimate was similar using fixed ratio compared to LLN in the larger and therefore more accurate LHS cohort. Diagnostic reversal occurred in 12.6% and 27.2% of subjects in these cohorts, and was commonest in subjects who quit smoking during the study. Diagnostic change was unusual after two confirmatory tests in people continuing to smoke.

If COPD is progressive, why does 'diagnostic instability' occur? As discussed by the Authors, respiratory infections and exposure to inhaled irritants can both cause transient changes in spirometry [3]. Moreover, the view that COPD is *always* progressive has been challenged [4]. Patients with asthma are characterised by variable airflow obstruction. Perhaps some patients had asthma? A self-report of physician diagnosed asthma was an exclusion to entry in the LHS, but not the CanCOLD study. However, removal of these subjects from the analysis did not materially affect the results and therefore this explanation seems unlikely.

The implication of these results is profound: a single post-bronchodilator spirometry test is insufficient to confirm or exclude COPD when the FEV_1/(F)VC ratio is close to the threshold, and certainty in diagnosis only becomes possible with more severe airflow obstruction. This is of relevance both in the clinic and in the context of clinical trials. Subjects with a fixed ratio ≤0.65 or LLN ≤0.2% had a 95% chance of retaining a COPD diagnosis at five years. For subjects above these limits, repeat testing is required, likely more than once in those who quit smoking.

This is not the first study to report such findings. Perez-Padilla [5] reported a similar diagnostic instability rate of 11.7% (using fixed ratio) in 2,026 patients enrolled in the PLATINO studies. Others have examined this too [6]. The current study is valuable because of its size and therefore measurement precision, the replication of findings, and the explicit description of appropriate cut-offs permitting security in diagnosis.

There are some further limitations. LHS and CanCOLD are both North American cohorts, where tobacco smoke is the principle inhaled toxin; globally COPD is a condition associated with biomass exposure. In addition, normal spirometry does not exclude other smoking related lung conditions such as emphysema [7]. However this study and others [5, 6] provides solid ground for a new paradigm in the diagnosis of COPD. We propose:

1. COPD requires the presence of *both* poorly reversible airflow obstruction and sufficient exposure to a recognised cause. GOLD [8] additionally emphasises the importance of symptoms.

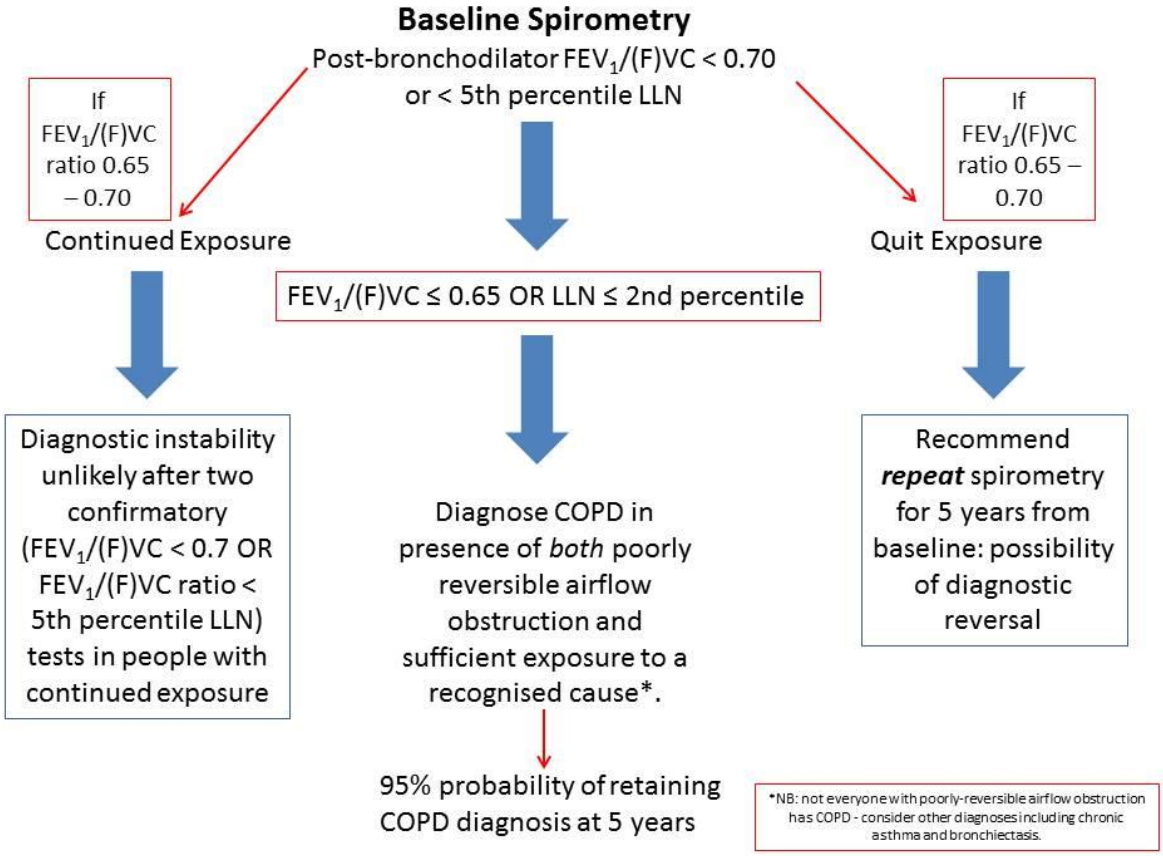
2. Not everyone with poorly reversible airflow obstruction has COPD - consider other diagnoses including chronic asthma and bronchiectasis.

3. People can have smoking-related lung disease with normal spirometry - consider whether there may be emphysema, chronic bronchitis, or smoking related interstitial disease.

4. Whichever approach is used, fixed FEV_1/(F)VC ratio or LLN, be wary of making and excluding the diagnosis of COPD in those people close to the threshold. A 'watch and repeat' policy may be best, especially for patients who successfully quit smoking (Figure 1).

GOLD states "the presence of a post-bronchodilator $FEV_1/FVC<0.70$ confirms the presence of persistent airflow limitation" [8]. Well, no, it doesn't. Caution is necessary around the threshold, whether it be LLN or fixed ratio. Hypertension treatment would not be started on the basis of one moderately elevated reading. We have to get the basics right in COPD too: accurate diagnosis, and exposure reduction for all.

Figure 1: A suggested approach to the diagnosis of COPD**.**



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