

## Impact of the ERS/ATS 2021 guidelines for lung function interpretation on assessing the response to biologics in asthma

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In 2021, the American Thoracic Society (ATS) and European Respiratory Society (ERS) updated standards for pulmonary function test interpretation [1]. Major changes regarding spirometry were:

1. The use of 80% predicted to define normal was no longer recommended. Instead, the general use of lower limit of normal (LLN) =5<sup>th</sup> percentile and upper limit of normal (ULN) =95<sup>th</sup> percentile was advocated (i.e., z-scores or percentiles). These guidelines now recommend the equations developed by the Global Lung Initiative (GLI) for referencing normal spirometry, diffusion capacity, and lung volumes. According to this, bronchial obstruction should be diagnosed when the forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio is not >5<sup>th</sup> percentile and FVC is >5<sup>th</sup> percentile. This recommendation is the result of an expert consensus, intending to identify, in a standardized and unbiased way, values that fall outside the range of those expected in the general population, and it implies accepting that it will result in 5% of healthy individuals being incorrectly classified as having an abnormal result. However, on the contrary, it overcomes the disadvantage of classifying a significant percentage of the elderly population as obstructive.

The newly formulated concept of “clinical remission” [2] and several tools developed to quantify the response to biologics in asthma [3] -such as the FEOS score [4]- incorporate lung function as one of the domains to be improved by treatment, and in all cases, FEV1 was chosen as the parameter for estimating bronchial obstruction. However, its interpretation is based on outdated recommendations. Considering that scores to measure response require simplicity, it will be mandatory to assume some limitation (spirometry is not a simple technique to perform and interpret), that most published studies on biological response use FEV1, and that this parameter has also traditionally been used in the estimation of lung function trajectories in asthmatics, we propose, at least, to replace the 80% predicted cut-off point by the z-score value  $-1.65$ .

2. Bronchodilator responsiveness (BDR) testing: changes in FEV1 and FVC following bronchodilator (the choice of protocol for administering bronchodilator is not specified) should be expressed as the percent change relative to the individual’s predicted value. A positive response is defined as an increase of  $>10\%$  of the predicted value. This approach minimizes sex and height differences in assessing BDR. However, some authors have argued that individuals who would have been considered responsive by the old criteria but not by the new (accounting for the impact of low baseline FEV1, which results in a more stringent method to classify the change) will be denied optimal treatment with bronchodilators [5]. Although we do not believe that the BDR test result is decisive in the choice of treatment for an asthmatic, it could modify the diagnostic process of the disease. Betancor et al. [6] have observed, in a real-life cohort of asthmatic patients, that only 26% of patients exhibited positive BDR using the new ERS/ATS 2022

recommendation and 33% using ERS/ATS 1991 BDR criteria. In accordance with these results, Li et al., in a sample of 4457 patients with asthma, found that the percentages of 2005-BDR+ and 2022-BDR+ were 63.32% and 52.84%, respectively [7]. This change in the definition of BDR is not likely to impact the estimation of response to biologics since it has been shown in real-life studies that its result is not a predictor of success or failure of the treatment [8].

Translating ERS/ATS 2021 recommendations into clinical practice requires a paradigm shift that will be easier if clinical studies reflecting their impact are available. Using the FEV1 z-scores as the therapeutic target for biological therapy, rather than the FEV1 percentage predicted, seems more reasonable, although it is not without limitations.

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