2022 ERS guidelines for asthma diagnosis in adults

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New adult asthma guidelines from the ERS: what do they cover and why should you use them?

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All clinical definitions of asthma recognise a characteristic set of symptoms that are periodic and vary in severity. However, symptoms (especially “wheeze”) can mean different things to patients, parents and doctors [1, 2], and there is widespread agreement that objective tests must be used. The other key part of the definition is variable airflow obstruction, and so tests that demonstrate exaggerated variability, such as repeated measurements, or pharmacological stimulation of broncho-constriction or dilation, have traditionally formed the core of asthma diagnostics. Many factors restrict widespread adoption of these tests (such as reliability, patient acceptability, and availability), and so alternatives are needed, either through development of cheaper or more user-friendly physiological tests, or detection of commonly associated traits such as atopy or type II inflammation. Many clinicians encounter difficulties in accessing these tests and so still rely on “clinical judgment”, despite evidence of misdiagnosis in around a third of cases [3, 4].

Two European Respiratory Society task forces were established in 2018 to identify and address the most important questions surrounding testing for asthma in children [5] and adults, and the adult group have published their findings in this issue of the European Respiratory Journal [6]. They have produced the first international recommendations to utilise a PICO (Patient, Index test, Comparator, Outcome) framework for identifying the questions of interest, and address them using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach, and the work it would have required must be applauded. The task force selected eight such questions and for each made a graded recommendation for or against adoption. They have also used the data gathered in this process, along with their clinical judgement, to propose a recommended diagnostic pathway.

The rationale for each of the PICO questions is given, and most are well justified and needed in light of their widespread clinical use and recommendation in other guidelines, although it is not clear why some tests (bronchodilator reversibility (BDR) testing, between-visit spirometry variability, response to inhaled corticosteroid treatment, allergy testing) were excluded in favour of others (the specific combination of fractional exhaled nitric oxide (FeNO), blood eosinophils and IgE, and the use of specific airway resistance and residual volume/total lung capacity ratio). The omission of BDR testing is particularly curious, given that it is included in the “gold standard” against which all other tests were judged.

This highlights the circular problem inherent in asthma guideline development, that the results of some tests (that demonstrate variable airflow obstruction) form part of the definition, and hence the gold standard. There is no good solution to this problem. Including the test elevates its specificity towards 100%, but excluding it increases the likelihood of false-negatives. Here, for example, the performance of bronchial challenge testing was tested against a reference standard that included only BDR, so patients with symptoms plus bronchial hyperresponsiveness but without reversible airflow obstruction (not an uncommon scenario and biasing against those with good lung function) would be classed as “non-asthma”,

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where any respiratory clinician faced with these results would almost certainly come to the opposite conclusion. The converse risk of including bronchial hyperresponsiveness in the reference standard (that false-positives are not identified) can be minimised with quality-controlled testing and reliable definitions of thresholds for positivity. As asthma is a variable disease, single time-point testing cannot be expected to ever have a high sensitivity and so, perhaps, the first aim should be for a clinically useful specificity (e.g. 95%), and test-order can be prioritised based on parameters such as sensitivity, feasibility, availability, patient acceptability and cost, many of which can be tailored to the healthcare setting.

Another difficulty in assessing asthma diagnostics are the varied cut-offs proposed for almost all key tests, including spirometry, peak flow variability, bronchial challenge testing and $F_eNO$. The task force has recommended adoption of a commonly cited threshold for BDR, requiring at least a 12% (and 200 mL) increase in forced expiratory volume in 1 s (FEV$_1$), whilst improvements in forced vital capacity (FVC) and FEV$_1$/FVC were not considered, even though they can give clinically useful information [7], and are obtained in the same manoeuvre. More importantly, the physiological rationale for such thresholds has moved on, with recently updated European Respiratory Society/American Thoracic Society guidance noting that reporting “change relative to baseline” in this way systematically disadvantages those towards the extremes of age and height, and so propose that the calculation should be made relative to an individual’s predicted lung function [7]. It is inevitable that data incorporated into the evidence synthesis have often not been generated to the same standards (or with the same type of equipment) as recommended by the time they are assimilated into guidelines. In the example given, should we use the new threshold for positive test in asthma diagnosis (a 10% change in % predicted FEV$_1$) or continue with one that perpetuates systematic bias and healthcare inequalities? This issue needs to be addressed through diagnostic cohort studies that collect continuous data across all relevant fields and so allow retesting of performance using varying thresholds.

A major benefit of the task force’s work is the patient perspectives that are offered on each question, and on the overall benefits of making an accurate diagnosis. They provide useful and novel insights to healthcare professionals involved in the care of people with asthma and should also be considered by those developing novel tests and pathways for asthma.

The group have also produced a pathway outlining the recommended sequence of tests, and it is probably this that will be the focus of the document for most. The entry-point into the path is notable by including people with “chronic or episodic symptoms at the time of testing”, and a similar term is used in each PICO (“episodic/chronic symptoms”); asthma though is characterised by variable symptoms, and the presence of chronic (but not episodic) symptoms would surely suggest other causes be considered first. The second part (“at the time of testing”) is particularly important and highlights that negative tests (especially of airflow obstruction) are only useful when the patient is symptomatic at the time of testing.

The pathway is necessarily as much influenced by the clinical experience and expertise of the authorship as by the outcomes of the PICO process, with BDR recommended in every patient with obstructive spirometry, and cut-offs for blood eosinophils and total IgE suggested, whilst neither were directly addressed by a PICO. Ultimately we need to know what the performance of the pathway, rather than individual tests, is. This will require data not currently available: how many patients “fail” at each step and therefore have to have further testing; how many remain “undiagnosed” at the end of the pathway; and how many of these subsequently turn out to have asthma (perhaps confirmed by testing when more symptomatic, e.g. at exacerbation)? Any given test’s performance downstream in a pathway will not be same as that in an unselected group of people with possible asthma. For example, if spirometry and BDR are tested first, then what we need to know is the performance of the next test in the subgroup who have failed those before. This again requires access to raw study data from prospective diagnostic studies that would allow testing of performance in designated subgroups.

Surrogates for type II airway inflammation ($F_eNO$, blood eosinophils and total IgE) are all included either directly or indirectly. The task force found that the specificity of high blood eosinophils and total IgE are better than that of $F_eNO$, even at the relatively high cut-off proposed (50 ppb), and so for blood eosinophils local cost-effectiveness analysis might be warranted to see if this test would be worth doing first, especially where $F_eNO$ is not available and especially where a recent result may be already on file. There will of course be other benefits of certain tests beyond use in diagnosis, such as $F_eNO$ and blood eosinophils, which may be useful in phenotyping and predicting poor outcomes [8].

For diagnostics, real-world performance must be considered against data from clinical trial settings. This is especially true of home peak expiratory flow monitoring. However, recent developments in electronic,
quality-checked spirometry may well revolutionise asthma diagnostics [9], both by keeping it out of healthcare settings and, perhaps more importantly, in delivering a test uniquely able to give a high sensitivity, with the patient able to detect airflow obstruction when symptomatic; in this situation normal, unobstructed expiratory flows would surely exclude the diagnosis of “asthma” as currently understood. Further, it will facilitate research into the true causes of episodic symptoms in such patients without asthma, a much-neglected group.

The rigorous approach to addressing specific questions of interest adopted here by the task force has generated new and useful insights that contribute to the ongoing effort to standardise the approach to the diagnosis of asthma across healthcare systems. I look forward to seeing how and where these guidelines are now implemented, and how they perform in comparison to other national and international recommendations. Improving the quality and accuracy of asthma diagnosis should now be the focus of future work across these different systems, to effect implementation and hopefully drive better asthma care.

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References