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1 A clinically significant bronchodilator response in children. How should it be measured? 2 Reply

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- 4 From the authors:

5 We thank F. Guezguez and H. Ben Saad for raising important questions on recommendations for assessing a 6 bronchodilator response (BDR) in children. The authors summarise how recommended outcome measures 7 and cut-offs for BDR in children vary between guidelines, and raise guestions about our study [1].

8 To clarify: our study did not focus on bronchodilator reversibility testing in children or compare different 9 outcome measures. Rather, we assessed the contribution of a detailed history and a variety of tests for 10 diagnosing asthma in children aged 6-16 years referred to pulmonary outpatient clinics. We compared the 11 diagnostic performance (sensitivity, specificity) of different commonly performed tests: skin-prick tests, 12 measurement of exhaled nitric oxide fraction (F_{ENO}), spirometry, bronchodilator reversibility and bronchial 13 provocation tests (BPT) by exercise, methacholine and mannitol against an asthma diagnosis from the 14 paediatric pulmonologist. Thus, we used tests, outcomes and cut-offs commonly recommended and used in 15 clinical practice. In addition, for examinations that provided a continuous (rather than a binary) output, such as forced expiratory volume in 1 s (FEV₁), BDR or F_{ENO} , we also assessed which cut-off distinguished best 16 17between those with and without asthma. We found that the combined sensitivity and specificity was highest for 18 reported symptoms (frequent wheeze, night-time awakening due to wheeze, and wheeze triggered by 19 pollen or pets). Among the tests, the area under the curve was highest for F_{ENO} and BPT by methacholine or 20 exercise, and lower for spirometry, bronchodilator reversibility and skin-prick tests.

21 F. Guezquez and H. Ben Saad ask how we had assessed FEV₁ increase: as percentage of the initial value, as 22 percentage of the predicted value, or as absolute increase. We calculated BDR as percentage increase of the 23 initial FEV₁ (in mL) using the following formula: (FEV₁ post-bronchodilator – FEV₁ pre-bronchodilator)/ FEV₁ 24 pre-bronchodilator. This is the most widely used method for calculating reversibility and recommended 25 by most guidelines [2-4]. FEV₁ pre- and post-bronchodilator was measured in triplicate and American 26 Thoracic Society/European Respiratory Society guidelines reproducibility criteria were applied [5]. Second, 27 they indicated that BDR can also be calculated for forced vital capacity and peak expiratory flow. 28 Although this is true, FEV₁ is the most widely recommended outcome, as it is less subject to cooperation 29 and has higher reproducibility [2, 3].

30 Third, they wondered what evidence we used to base our cut-off levels on. The 12% cut-off is 31 recommended in all recent guidelines, but derives from studies in adults, expert opinion, or studies that 32 compared severe asthmatics with healthy children. Recent population-based studies have questioned this 33 cut-off for the paediatric population [6, 7]. In our study of children seen for evaluation of possible asthma in 34 paediatric outpatient clinics, a cut-off of 10% had the highest combined sensitivity and specificity. 35 However, we want to stress that cut-off levels for diagnostic tests that produce an outcome on a 36 continuous scale are artificial and an oversimplification. We lose information if we force a continuous 37 measure into a binary one. There is a trade-off between sensitivity and specificity, and depending on the 38 clinical question, higher or lower cut-offs can be preferable. In general, the further away a result is from the 39 mean of the frequency distribution in healthy children, the more likely it is that it is pathological. There is 40 no such thing as a "true" cut-off that distinguishes unequivocally between healthy and diseased. For clinical 41 application, a cut-off is often helpful, but factors such as pre-test probability, place of the test in the 42 diagnostic algorithm, and costs must also be considered.

In conclusion, we fully agree with F. Guezguez and H. Ben Saad that more research is needed to evaluate
the usefulness of diagnostic tests for asthma in children. We also agree that cut-offs should be critically
questioned and defined based on evidence from the patient population of interest (*i.e.* children suspected
with asthma) and not based on studies in adults or on expert opinion.

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62 63 64 65 66 67 68 69 71 72 73 775 77 78 81 823 84 858 87 88	 References: de Jong CCM, Pedersen ESL, Mozun R, <i>et al.</i> Diagnosis of asthma in children: the contribution of a detailed history and test results. <i>Eur Respir J</i> 2019; 54: 1901326. NICE. Guideline Asthma Diagnosis and Monitoring. www.nice.org.uk/guidance/ng80/resources/asthma-diagnosis- monitoring-and-chronic-asthma-management-pdf-1837687975621 Date last updated: November 2017, December 2019. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. <i>J Allergy Clin Immunol</i> 2007; 120: Suppl. 5, S94–S138. Pellegrino R, Decramer M, van Schavck CP, <i>et al.</i> Quality control of spirometry: a lesson from the BRONCUS trial. <i>Eur Respir J</i> 2005; 26: 1104–1109. Quanjer PH, Stanojevic S, Cole TJ, <i>et al.</i> Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. <i>Eur Respir J</i> 2012; 40: 1324–1343. Murray C, Foden P, Lowe L, <i>et al.</i> Diagnosis of asthma in symptomatic children based on measures of lung function: an analysis of data from a population-based birth cohort study. <i>Lancet Child Adolesc Health</i> 2017; 1: 114–123. Tse SM, Gold DR, Sordillo JE, <i>et al.</i> Diagnostic accuracy of the bronchodilator response in children. <i>J Allergy Clin Immunol</i> 2013; 132: 554–559.