Asthma Diagnosis and Monitoring

Consultation on draft guideline
Stakeholder comments table

28/01/2015-11/03/2105

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
Aerocrine	Full	31	32-34	We are not quite sure how to interpret this sentence on lines 32-34; i.e., the relationship between FENO and atopy. Fractional exhaled nitric oxide primarily signals local T helper cell type 2- driven inflammation in the bronchial mucosa. Thus, exhaled nitric oxide is not a marker of atopy but rather of its consequence; inflammation caused by exposure to allergens and a marker of allergen induced phenotype of asthma.	Thank you for your comment. We think you are referring to page 13 (not 31), lines 32-34 of the full guideline and have responded on this basis. We have amended this paragraph which now reads "Testing for airway inflammation is increasingly used as a diagnostic strategy in clinical practice. This includes measuring fractional exhaled nitric oxide (FeNO). However, there is some uncertainty about both the sensitivity and specificity of FeNO, particularly as to whether it can distinguish individuals with allergen induced airways inflammation without airways hyperreactivity from individuals with asthma."
Aerocrine	Full	49	2 - 5	Please, consider to include publications by "Pérez-de-Liano LA et al. Exhaled nitric oxide predicts control in patients with difficult-to-treat asthma. Eur Respir J 2010;35:1221–7." to support identification of difficult to treat asthma. In addition, please consider Malinovischi A et al. FeNO as a predictor of asthma control improvement after starting inhaled steroid treatment. Nitric Oxide. 2014 Aug 31;40:110-6."	Thank you for your comment. Difficult to treat asthma is outside scope. For the review for the effectiveness of FeNO monitoring, only RCT studies were included assessing the effectiveness of treatment guided by FeNO monitoring on patient outcomes. Observational studies were not included in this review.
Aerocrine	Full	131	3-5	Please, consider to include publication by "Zietkowski et al. Comparison of Exhaled Nitric Oxide Measurement	Thank you for your comment. The reference mentioned was included in the clinical evidence

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				With Conventional Tests in Steroid-Naive Asthma Patients. Investig Allergol Clin Immunol 2006;16(4): 239-246." In this study the authors compared measured FENO from healthy, allergic and non-allergic individuals. The study showed that predefined normal values (i.e. in healthy individuals) for FENO (< 20 ppb) were found more often in the group of patients with non-allergic asthma. Therefore, we suggest that in adults' (16 years and older) cut-off of 30 ppb would be more consistent to support diagnosis of asthma.	review as one of the studies used to compare FeNO levels in people with asthma vs other respiratory conditions or healthy individuals (appendix J table 203). This information was considered by the GDG when setting the FeNO level, alongside diagnostic accuracy information from the cross-sectional studies. A cut-off of greater than or equal to 40ppb was chosen in adults as this cut-off value has a high sensitivity and specificity and is above the range of FeNO levels observed in a population of mixed respiratory symptoms without a diagnosis of asthma.
Aerocrine	Full	131	14	We believe that cut-off values in children should be lower. Please, consider to include publications by "Malmberg LP et al. Exhaled nitric oxide rather than lung function distinguishes preschool children with probable asthma. Thorax 2003;58:494-99." and Wan et al "Asthma diagnosis and severity monitoring in primary schoolchildren: Essential role of sequential testing of exhaled nitric oxide" Allergol Immunopathol (Madr) 2014 Sep-Oct;42(5):439-43. We would also kindly ask you to re-consider to include publication by Sivan Y et al. The use of exhaled nitric oxide in the diagnosis of asthma in school children. J Pediatr. 2009;155(2): 211-6. Therefore, we suggest that in in children (5-16 years of age) cut-off of < 25 ppb would be more consistent to support diagnosis of asthma.	Thank you for your comment. Malmberg 2003 was excluded as the diagnostic accuracy was based on the discrimination between children with probable asthma and healthy controls. Studies of this design were excluded as they do not represent the population in which the test will be used clinically (people with respiratory symptoms) and inclusion of healthy controls may lead to over estimations of specificity. Wan 2014 provides the FeNO level in children with wheeze and allergy, not the protocol population of asthma diagnosed by a physician with an objective test. Sivan 2009 was excluded as the flow rate for the FeNO measurement was not reported in the paper. The flow rate used will determine the accuracy of the test and papers not

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					reporting this information were excluded.
Aerocrine	Full	143	Other considerations	Some children need several attempts to perform spirometry successfully. In these cases the FENO measurements should be performed first because the order of respiratory tests in children with asthma may have a modest effect for the FENO measurements. However, if the child completes spirometry easily the order of respiratory tests does not need to be considered. Please, consider to include publications by "Eckel SP et al. Spirometry effects on conventional and multiple flow exhaled nitric oxide in children. J Asthma 2014 Aug 28:1-7." and Garriga, T et al. Spirometric maneuvers and inhaled salbutamol do not affect exhaled nitric oxide measurements among patients with allergic asthma. Respiration 2012;83:239–244.	Thank you for your comment. The papers suggesting an effect of salbutamol or spirometry on FENO tend to be older papers and do not necessarily use modern FENO equipment. The effect is not present in all papers and when present is typically small.
Aerocrine	Full	229	12-17	For monitoring inflammation in asthma, please, consider "Paro-Heitor ML et al. Exhaled nitric oxide for monitoring childhood asthma inflammation compared to sputum analysis, serum interleukins and pulmonary function."Pediatr. Pulmonology 2008 Feb;43(2):134-41."	Thank you for your comment. For the review for the effectiveness of FeNO monitoring, only RCT studies were included assessing the effectiveness of treatment guided by FeNO monitoring on patient outcomes. Observational studies were not included in this review.
Aerocrine	Full	229	23-24	Several studies have shown that increased FeNO relates to future risk in terms of exacerbations and decline in lung function. Please, consider to include	Thank you for your comment. Prognostic studies were not included in this review. The GDG acknowledged that prognostic studies have shown

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				publications by "Gelb AF et al. Role of spirometry and exhaled nitric oxide to predict exacerbations in treated asthmatics. Chest 2006; Jun;129(6):1492-9." and "Zeiger RS et al. Elevated exhaled nitric oxide is a clinical indicator of future uncontrolled asthma in asthmatic patients on inhaled corticosteroids. J Allergy Clin Immunol, 2011. 128 (2): 412-4.	increased FeNO to be associated with future risk. However, the GDG wished to evaluate the effectiveness of monitoring FeNO to guide treatment on patient outcomes in an RCT design.
Aerocrine	Full	229	27-32	When monitoring asthma sequential FeNO measurements may be helpful and improve outcomes with regard to indicating improvement in asthma control over time. Please, consider to include publications by "Ozier A et al. Control maintenance can be predicted by exhaled NO monitoring in asthmatic patients. Respir Med 2011 Jul;105(7):989-96." and " Michils A et al. Exhaled nitric oxide and asthma control: a longitudinal study in unselected patients. Eur Respir J 2008; 31: 539–546."	Thank you for your comment. For the review for the effectiveness of FeNO monitoring, only RCT studies were included assessing the effectiveness of treatment guided by FeNO monitoring on patient outcomes. Observational studies were not included in this review.
Aerocrine	Full	233	Other considerations	We would like to bring to your attention a study where FENO was assessed for the management of asthma in a subgroup of asthmatics, namely pregnant women. Please, consider the publication by "Powell H et al. Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial. *Lancet* 2011; 378: 983–90." In this study Asthma exacerbations during pregnancy were reduced with a validated FENO-	Thank you for your comment. We have now included Powell 2011 in the FeNO for monitoring review. However, prenatal prevention of asthma is outside scope and therefore data from Mattes 2014 cannot be considered.

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				based treatment algorithm. We would also like you to consider the follow up study by Mattes J et al. Prenatal origins of bronchiolitis: protective effect of optimised asthma management during pregnancy. Thorax 2014;69(4):383-4. This study showed that optimised management of asthma during pregnancy may reduce recurrent episodes of bronchiolitis in infancy, which could potentially modulate the risk to develop or the severity of emerging childhood asthma.	
Alder Hey Children's Hospital, Liverpool	Full	General	General	We feel the algorithm proposed is untested and in our experience will underdiagnose asthma – for example very few children (even in our most difficult cohort) have an FEV1 <70% predicted	Thank you for your comment. The GDG acknowledges that there is a paucity of diagnostic test accuracy data in children and hence made a high priority research recommendation to elucidate the best diagnostic pathway. The GDG has amended the recommendations for FeNO and BDR from 'offer' to 'consider' in children to reflect the evidence base. A footnote on the diagnostic cut-off values for children has also been added to the recommendations on spirometry and BDR. Furthermore, the GDG has added a caveat to the diagnostic algorithm for children to account for those children who are unable to perform objective tests from age 5 onwards that the principles in recommendation 1.2.1 should be followed until the child is old enough to perform objective tests adequately.

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Alder Hey Children's Hospital, Liverpool	Full	General	General	We feel the data for FENO are not fully tested or validated in children and further research is required to evaluate the most appropriate cutoff, should FENO be used as a diagnostic tool	Thank you for your comment. The GDG acknowledges that there is a paucity of diagnostic test accuracy data in children and hence made a high priority research recommendation to elucidate the best diagnostic pathway. The GDG has amended the recommendations for FeNO and BDR from 'offer' to 'consider' in children to reflect the evidence base. A footnote on the diagnostic cut-off values for children has also been added to the recommendations on spirometry and BDR. Furthermore, the GDG has added a caveat to the diagnostic algorithm for children to account for those children who are unable to perform objective tests from age 5 onwards that the principles in recommendation 1.2.1 should be followed until the child is old enough to perform objective tests adequately.
Alder Hey Children's Hospital, Liverpool	Full	General	General	Setting up community-based physiology testing services in children will require investment, and we feel such services must be under the governance of the local regional centre with expertise in paediatric respiratory physiology . There is a drive to improve and standardise physiology services in children (as per ATS/ERS guidance) and GP practices will require a lot of support to set up such facilities	Thank you for your comment. The primary aim of this clinical guideline was to produce the most clinically and cost effective way to diagnose asthma accurately. The GDG acknowledges that the implementation of some objective tests in primary care will require initial investment and training. However, the health gains and improvements in patient outcomes have been shown to be clinically effective as well as cost effective for the NHS;

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					please see the health economic analysis in appendix M. The NICE Implementation team will produce support materials to facilitate uptake of the guideline into clinical practice. Furthermore, the GDG do not consider that all of the recommendations are new to clinical practice, for example, spirometry services should be available in all GP practices already. The only new objective test recommended in the guideline is a FeNO test; the GDG consider that performing a FeNO test is much easier than performing spirometry. FeNO has been shown to be cost effective by both the original health economic model developed as part of this guideline's cost effectiveness analysis and by the NICE DAP health economic model.
Alder Hey Children's Hospital, Liverpool	Full	General	General	The use of 'trial of therapy' is well recognised as a crucial element of diagnosis of asthma in children, and the current guidance does not recognise this	Thank you for your comment. The GDG disagrees that trial of treatment should be given on the basis of symptoms alone. Trials of treatment are certainly used traditionally, but we note that the BTS/SIGN developers found no strong evidence in their support; the use of a trial of treatment is graded as a Good Practice Point for children and a Grade C recommendation for adults within that Guideline. A counter view is that they can lead to misdiagnosis when a natural improvement in symptoms coincides with, and is spuriously attributed to, introduction of

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					asthma therapy. The proposed diagnostic sequence allows their use in cases of genuine doubt (see algorithms B1 & C) but encourages the use of more objective tests beforehand. The diagnostic endpoints do factor in reviewing the diagnosis of asthma based on response to treatment.
Alder Hey Children's Hospital, Liverpool	Full	General	General	The NICE guidance is actually very different from the BTS/SIGN guideline on asthma – the latter does not include BDR or FENO	Thank you for your comment.
RCP NRAD 2014 Clinical Lead	Full	General	General	In my opinion, these new guidelines don't address the issues raised in the NRAD – particularly the fact that guidelines were not implemented in half of those who died and that diagnosis was so poor and that those at risk were not identified. The proposed guidelines are fine for those working in high powered academic research institutions, however they miss the mark for jobbing Gps at the coalface. To suggest that spirometry is essential for diagnosis of airflow limitation fails to acknowledge that asthma is characterised by recurrent intermittent symptoms. Are NiCE seriously suggesting that asthma can only be	Thank you for your comment. The GDG is aware of the NRAD's key findings. However, we would point out that these were not published (May 2014) until development of this guideline was advanced, and that addressing all the important messages that fell out of NRAD was not, and could not, have been an aim of this guideline process. We do not agree that inappropriate treatment (excess SABA) is any more likely to be prescribed through following our diagnostic algorithm than it is at present – it happens currently as NRAD ably demonstrated. A major aim of this clinical guideline was to produce

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				diagnosed at a time when a patient presents with airflow limitation ?? This seems to be the case . In reality, many people are normal at the time of consulting – especially if they have taken bronchodilators before attending. So it seems you want Gps to do serial spirometry – which isn't going to happen. What will happen is that people will be prescribed masses of SABA, as in the NRAD, without a diagnosis ever being made. Similarly its fine for the handful of units with FeNO – are you seriously suggesting we should all have the equipment, and that this will solve the problems? Im my opinion, from the NRAD, we need a very simple guideline: Diagnose asthma if: 1. A patient with a suggestive history responds to asthma treatment; 2. Has evidence of reversible airflow limitation (serial PEF or reversible quality assured spirometry And if there is a poor response to treatment, or the person needs more than 6 SABa's a year or the person remains poorly controlled, then refer to a tertiary care unit where all the tests mentioned in the draft guideline can be performed.	the most clinically and cost effective way to diagnose asthma accurately. The GDG acknowledges that the implementation of some objective tests in primary care will require initial investment and training. However, the health gains and improvements in patient outcomes have been shown to be clinically effective as well as cost effective for the NHS; please see the health economic analysis in appendix M. The NICE Implementation team will produce support materials to facilitate uptake of the guideline into clinical practice. Furthermore, the GDG do not consider that all of the recommendations are new to clinical practice, for example, spirometry services should be available in all GP practices already. The only new objective test recommended in the guideline is a FeNO test, however, the GDG consider that performing a FeNO test is much easier than performing spirometry. FeNO has been shown to be cost effective by both the original health economic model developed as part of this guideline's cost effectiveness analysis and by the NICE DAP health economic model. We acknowledge that it will take time to make FENO widely available, but failing to recommend it would

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				This in my opinion, will result in a massive change. I also suggest see the new GINA Guideline at www.ginasthma.org which includes an implementation plan	lead to even greater delays in establishing its role. The diagnosis of asthma can be made within our recommendations without needing multiple spirometry measurements as you suggest. Spirometry is recommended as the first objective test in the diagnostic pathway because the definition of asthma includes airway obstruction and therefore this test is necessary, but as recommendation 1.2.2 clearly states that the diagnosis of asthma should not be made on the basis of any single diagnostic test alone. Please refer to the diagnostic algorithms which show the series of objective tests that should be conducted thereafter if spirometry is non-obstructive. The combination of objective tests in the diagnostic pathway will rule out or rule in asthma depending on each test's outcome which account for the intermittent nature of asthma symptoms. The diagnostic pathway is designed not to leave people on asthma treatment without a confirmed diagnosis. The recommendations for diagnostic outcome 'suspect asthma' state 'Do not rule out other diagnoses if symptom control remains poor after

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					treatment. Review the diagnosis of asthma'. This diagnostic outcome allows for people to be re-diagnosed if their symptoms do not improve with asthma treatment and investigated for other diagnoses. The GDG disagrees that the implementation of the diagnostic algorithm is prohibitively complex. Patients who present to their GP with mild symptoms of asthma can perform spirometry, BDR and FeNO tests during a follow-up appointment with the practice nurse to get a positive diagnosis of asthma. A small proportion of patients with diagnostic uncertainty will go through the longer route in the diagnostic pathway in order to obtain further objective testing evidence of asthma. The GDG considered that patients with intermittent symptoms should be called back for further review.
Association for Respiratory Technology & Physiology (incorporating the	Full	40 General 92	Table General 24	***Diagnostic algorithm B1*** *From diagnostic algorithm A: adults and young people older than 16 with obstructive spirometry (FEV_1/FVC ratio less than 70%)* *Offer a bronchodilator reversibility (BDR) test.* *Regard an improvement in FEV_1 of 12% or more, together with an increase in volume of 200 mL or*	Thank you for your comment Technically we agree, you are correct. However, you will also be aware of the numerous implementation difficulties around use of spirometry in practice, and these include problems of interpretation. The GDG feel that many users of the guideline would have difficulty with a recommendation expressed in terms of standardised residuals, whereas the FEV1/FVC ratio is widely

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views of the Global Lung Initiative Group)				*more, as a positive test.* We would like to discourage the practice of expressing FEV_1 as a percentage of predicted. We realise it is standard procedure, but its use leads to significant age bias[72,83]. This is because percent predicted is only appropriate if the scatter around the predicted value is proportional to the predicted value, i.e. the coefficient of variation (CoV) is constant, which it is not. The use of percent predicted was introduced in 1959,[105] without any clinical validation. This rule was repeatedly shown to be flawed and associated with an age bias[70,106-112]. In fact Sobol wrote: "Nowhere else in medicine is such a naïve view taken of the limit of normal"[107]. Rather than expressing the FEV_1 as a percentage of predicted, it should be expressed as the number of standard deviations it differs from predicted, i.e. as a z-score.[113] This removes the age bias, and the calculation is available in software of all the major spirometer manufacturers.	understood. Using the ratio may lead to a small increase in the number of older people who proceed to reversibility testing, but asthma is not being diagnosed on the basis of an obstructive ratio alone so should not lead to any increase in misdiagnosis in the older population.

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				The statement that FEV_1 is considered to be the "gold standard" measurement of airways obstruction is incorrect. Firstly, it contradicts the recommendations about diagnostic spirometry in the NICE guidelines, where the FEV_1/FVC is recommended instead. Secondly, large international organisations regard a low FEV_1/FVC as the hallmark of airflow limitation, not the FEV_1.	
Association for Respiratory Technology & Physiology (incorporating the views of the Global Lung Initiative Group)	Full	General		We would like to object very strongly to the publicity that NICE put out at the launch of this consultation process, when clearly the content of the final guideline was not complete and hence open to this consultation. This was captured by the media who as usual distorted the public's perception of asthma and its treatment and may have emphasised guidance which we actually now believe to be incorrect. We would like to discourage NICE from this media hype in future draft consultation guidance as it is counter-productive in informing the public about best practice linked to the evidence base. Publicity after the final version is naturally acceptable. Can you confirm that NICE will no repeat this practice in	Thank you for your comment. This issue has been referred to the NICE press office for consideration.

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				future?	
Association for Respiratory Technology & Physiology (incorporating the views of the Global Lung Initiative Group)	Full	42	Table	***Diagnostic algorithm C*** *From diagnostic algorithm A: children aged 5-16 years undertake spirometry* ** Obstructive spirometry: FEV_1/FVC ratio less than 70%. Offer a bronchodilator reversibility (BDR) test. Regard an improvement in FEV_1 of 12% or more as positive.* ** Normal spirometry: FEV_1/FVC ratio is 70% or more.* The lower limit of the FEV_1/FVC ratio in the NICE guideline is regarded as being 70%, irrespective of age. However, there is overwhelming evidence that the lower limit is not constant but declines with age, irrespective of ethnic group.[1-90] This is enshrined in many international recommendations: the European Community for Coal and Steel (ECCS),[8,69] ECCS and European Respiratory Society (ERS),[70] American Thoracic Society,[92] and most recently in a report of the Global Lung Function Initiative, endorsed by the European Respiratory Society, American Thoracic Society	Thank you for your comment. We agree that using a fixed ratio of 70% to define obstruction will result in misclassification in a few children, particularly the youngest. However, as with adults there is a balance to be struck between scientific accuracy and usability of the guideline, and the GDG took into account the widespread acceptance of 70% as a threshold value for normality. Moreover, they found no evidence in children for the diagnostic value of FEV1/FVC ratio, nor for bronchodilator reversibility, and the recommendations are therefore based on extrapolation from adult data. The GDG acknowledges that there is a paucity of diagnostic test accuracy data in children and hence made a high priority research recommendation to elucidate the best diagnostic pathway. The GDG has amended the recommendations for FeNO and BDR from 'offer' to 'consider' in children to reflect the evidence base. A footnote on the diagnostic cut-off values for children has also been added to the recommendations on spirometry and BDR. Furthermore, the GDG has added a caveat to the diagnostic algorithm for children to account for those

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				(ATS), Australian and New Zealand Society of Respiratory Science, Asian Pacific Society for Respirology, Thoracic Society of Australia and New Zealand, and the American College of Chest Physicians.[72] The ATS and the ERS have specifically indicated that the use of a fixed ratio for FEV_1/FVC underestimates airflow limitation in children, adolescents and young adults, and overestimates it in adults aged over 40.[72,92-93] In the past one might have argued that appropriate "lower limits of normal" (LLN) were either not available or too complicated to calculate. However in the recent past numerous publications have provided reference limits, and the ready availability of built-in spirometry reference software obviates the need to perform calculations or consult tables.[5-6,22,30,46,72,83] Special mention needs to be made of two publications, which for the first time provided prediction equations covering the age range from 4-80[83] years and 3-95 years.[72] They showed that the coefficient of variation (CoV) of spirometry varies with age, being largest in the youngest	children who are unable to perform objective tests from age 5 onwards that the principles in recommendation 1.2.1 should be followed until the child is old enough to perform objective tests adequately.

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<tr><td></td><td></td><td></td><td></td><td>children and the oldest adults. This increases the difference between the predicted value and the LLN, as illustrated in figure 1, which are based on 25,720 and 31,399 observations from healthy non-smoking white males and females, respectively.[72] The table shows that before age 45 the LLN for FEV_1/FVC is well above 70%, and after age 45 well below it. All major spirometer manufacturers have included in their software the GLI equations endorsed by the above six international respiratory societies[72], so that proper cut-off criteria are available universally.
<table>
<tr><td colspan="5">LLN for FEV_1/FVC as a function of age</td></tr>
<tr><td>Sex</td><td>3 yr</td><td>20 yr</td><td>45 yr</td><td>90 yr</td></tr>
<tr><td>Male</td><td>84.0%</td><td>73.8%</td><td>69.4%</td><td>61.7%</td></tr>
<tr><td>Female</td><td>85.5%</td><td>76.8%</td><td>70.3%</td><td>60.4%</td></tr>
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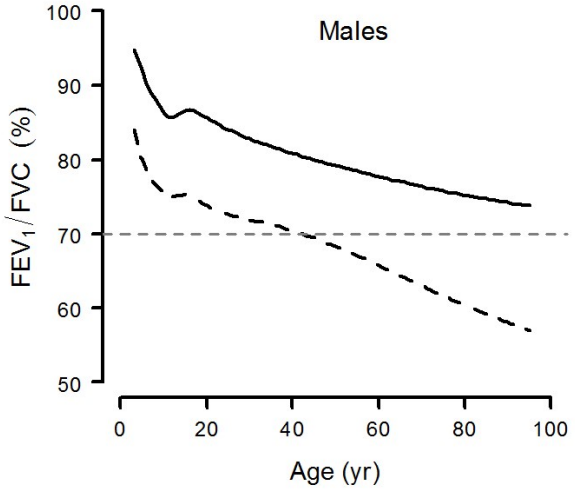
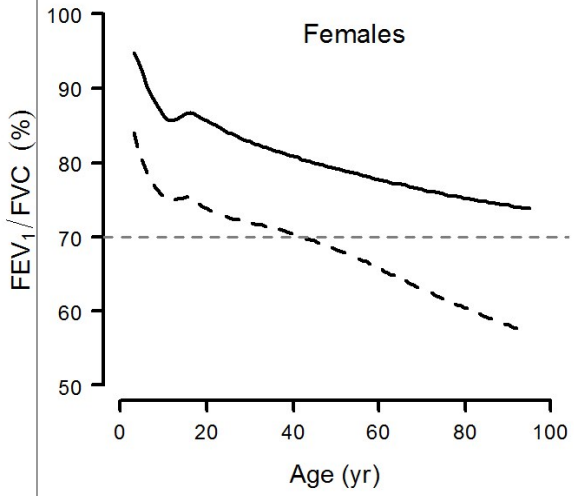
				 Figure 1 – Predicted FEV_1/FVC[72] (solid line) and lower limit of normal (dashed line) as a function of age for a white males and females of average height. Of the females 14,078 were aged 3-<20 yr, and 17,321 ≥20-95 yr. Corresponding figures for males 14,500 and 11,220, respectively. **Clinical validity of 70% lower limit**	

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				In clinical medicine the 95% reference range for analytes, derived from healthy subjects, is used universally for diagnostic purposes. In respiratory medicine only a low FEV_1/FVC ratio is regarded as diagnostically relevant, and by convention the LLN is therefore fixed at the 5^{th} centile of the distribution in a reference population, leading to a 5% false positive rate. However, some argue that in respiratory medicine a statistically-based LLN using data on healthy lifelong non-smokers does not necessarily delineate a cut-off for clinical purposes. Several studies have addressed the question whether an FEV_1/FVC ratio below 70% but above the LLN is associated with respiratory disease. This question is relevant for subjects above 45 years of age, where the focus of studies has been primarily on COPD. Since those studies used the same fixed ratio as that recommended in the NICE guidelines, the results are however relevant to the current discussion. A summary of findings with respect to what was found for such subjects, who would be diagnosed as having COPD grade 1 according to the guidelines of the	

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				GOLD consortium,[94] is given below. In asymptomatic subjects, an FEV_1/FVC above the LLN but below 70% was neither associated with premature death[95-96] nor with an abnormal decline in FEV_1, respiratory care use, or quality of life compared with a reference group.[97] It was not associated with premature death or respiratory symptoms.[98] The adjusted hazard ratio for premature death did not differ significantly from one.[99] Only GOLD stage I with FEV_1/FVC below the LLN was associated with increased risk of death.[98-99] The use of the LLN for both FEV_1/FVC and FEV_1, rather than a fixed ratio and 80% predicted, identified persons with an increased risk of death and prevalence of respiratory symptoms.[100] "After correction for potential confounders, only severe COPD as defined by the [British Thoracic Society] criteria was still associated with mortality."[101] An FEV_1/FVC below 70% but above the LLN was	

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				not associated with an accelerated decline in FEV_1.[102-103] We conclude that respiratory disease or death from respiratory causes was only associated with an FEV_1/FVC ratio below the LLN. This is in keeping with a report from the BOLD study.[104] Ideally one should also study whether in patients under age 45 an FEV_1/FVC ratio above 70% but below the LLN is associated with respiratory disease. Unfortunately, we could find no studies addressing this.	
Association for Respiratory Technology & Physiology (incorporating the views of the Global	Full	204	9-13	*Evidence of airways obstruction is a poor prognostic factor for the outcome of asthma and a low FEV_1 identifies patients at risk of asthma exacerbations, independent of symptom levels, especially if FEV_1 is <60% predicted. FEV_1 is considered to be the "gold standard" measurement of airways obstruction due to its accurate, well standardised measurements, repeatability and reliable reference values.*	Thank you for your comment. Technically we agree, you are correct. However, you will also be aware of the numerous implementation difficulties around use of spirometry in practice, and these include problems of interpretation. The GDG feel that many users of the guideline would have difficulty with a recommendation expressed in terms of standardised residuals, whereas the FEV1 as a percent of predicted is widely understood.

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<tr><td>Lung Initiative Group)</td><td></td><td></td><td></td><td>We would like to discourage the practice of expressing FEV_1 as a percentage of predicted. We realise it is standard procedure, but its use leads to significant age bias[72,83]. This is because percent predicted is only appropriate if the scatter around the predicted value is proportional to the predicted value, i.e. the coefficient of variation (CoV) is constant, which it is not. Thus the CoV for FEV_1 in males, and the associated LLN[72], is as in the table below.

<table>
<tr><td>Age (years)</td><td>3</td><td>20</td><td>45</td><td>90</td></tr>
<tr><td>CoV (%)</td><td>14.1</td><td>12.0</td><td>13.8</td><td>21.3</td></tr>
<tr><td>LLN (% predicted)</td><td>76.8</td><td>80.3</td><td>77.3</td><td>65.0</td></tr>
</table>

The use of percent predicted was introduced in 1959,[105] without any clinical validation. This rule was repeatedly shown to be flawed and associated with an age bias[70,106-112]. In fact Sobol wrote: "Nowhere else in medicine is such a naïve view taken of the limit of normal"[107]. Rather than expressing the FEV_1 as a percentage of predicted,</td><td></td></tr>
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				it should be expressed as the number of standard deviations it differs from predicted, i.e. as a z-score.[113] This removes the age bias, and the calculation is available in software of all the major spirometer manufacturers. The statement that FEV_1 is considered to be the "gold standard" measurement of airways obstruction is incorrect. Firstly, it contradicts the recommendations about diagnostic spirometry in the NICE guidelines, where the FEV_1/FVC is recommended instead. Secondly, large international organisations regard a low FEV_1/FVC as the hallmark of airflow limitation, not the FEV_1.	
Association for Respiratory Technology & Physiology (incorporating the views of the Global	Full	95	20-26	**Bronchodilator response** The NICE recommendation is to regard a 12% increase in FEV_1 (and >200 mL in those $\geq$20 years) as a positive bronchodilator response. This criterion, where the 12% increase was relative to the predicted value, was first published in 1993[70]. An increase relative to the initial value is to be frowned upon, as it is affected by regression to the mean; also 12% of the initial value is much more	Thank you for your comment. All the evidence that the GDG identified expressed change as absolute values, or as percent change. The problem you identify was recognised by the GDG, but given that this was the available evidence they made a recommendation based on it, but incorporating absolute change **and** percent change to offset the problem of a small initial value.

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Lung Initiative Group)				easily reached if the initial value is small. Further research is required in this field, particularly when assessing BDR in children.	
Association for Respiratory Technology & Physiology (incorporating the views of the Global Lung Initiative Group)	Full	87	14	***Reference values*** The NICE recommendations refer to evidence using percent of predicted FEV1, but there is no clear mention of which reference ranges to use. There is large variation in published population based "normal" lung function reference values. However in recent years the GLI Reference[121] ranges have been adopted by most global respiratory organisations as being the most appropriate ranges from ages 3-95. The document should refer to these reference ranges for UK children of different ethnic backgrounds. The need to take ethnicity into account is enshrined in many international recommendations: the European Community for Coal and Steel (ECCS),[8,69] ECCS and European Respiratory Society (ERS),[70] American Thoracic Society,[92] and most recently in a report of the Global Lung Function Initiative,	Thank you. None of the recommendations are based on percent predicted FEV1. Some of the papers in the evidence base refer to this; the reference ranges are those used by the relevant investigators.

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				endorsed by the European Respiratory Society, American Thoracic Society (ATS), Australian and New Zealand Society of Respiratory Science, Asian Pacific Society for Respirology, Thoracic Society of Australia and New Zealand, and the American College of Chest Physicians.[72]	
Association for Respiratory Technology & Physiology (incorporating the views of the Global Lung Initiative Group)	Full	General		***Lung Function Training (Spirometry, FeNO)*** Our other area of concern relates to healthcare professionals who may undertake some of these diagnostic investigations. Without appropriate training, such tests in the wrong hands, will result in over and under-classification of lung abnormalities. It is vitally important that respiratory physiological investigations are performed to appropriate quality standards. These standards are maintained through effective training of healthcare professionals who ensure: • the equipment being used meets quality standards through effective verification	Thank you. We agree that diagnostic tests, like treatment procedures, should only be performed by appropriately trained personnel and with correctly standardised and maintained equipment.

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				ensuring correct functionality and data output • identification of problems with test performance technique by the patient ensuring reproducibility of results • appropriate interpretation using evidence-based analysis Without these standards in place and appropriate training the data produced are ineffective at detecting abnormalities of physiology. References: 1. Berglund E, Birath G, Bjure J, Grimby G, Kjellman I, Sandquist I, Söderholm B. Spirometric studies in normal subjects. I. Forced expirograms in subjects between 7-70 years of age. Acta Med Scand 1963; 173: 185-192. 2. Bjure J. Spirometric studies in normal subjects. IV. Ventilatory capacities in healthy children 7-17 years of	

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Association for Respiratory Technology & Physiology (incorporating the	Full	General	General	Furthermore , we would particularly like to object very strongly to the publicity that NICE put out at the launch of the consultation process, when clearly the content of the final guideline was not complete and hence open to consultation. This was captured by the media	Thank you for your comment. This issue has been referred to the NICE press office for consideration.

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views of the Global Lung Initiative Group)				who as usual distorted the public's perception of asthma and its treatment and may have emphasised guidance which we actually now believe to be incorrect. We would like to discourage NICE from this media hype in future draft consultation guidance as it is counter-productive in informing the public about best practice linked to the evidence base. Can you confirm that NICE will no repeat this practice in future?	
Association of Respiratory Nurse Specialists	Full	General	General	The Association of Respiratory Nurse Specialists (ARNS) are fully committed to supporting better diagnosis and best standards, particularly around the issues highlighted within the National Review Asthma Deaths (NRAD)report. Asthma is serious and unnecessary deaths have to stop, we support the NRAD report, which argues that the basics of asthma care needs improving.	Thank you for your comment.
Association of	Full	General	General	Following the draft publication, we have sought the views of our 1000 members across the UK and received	Thank you for your comment. The primary aim of this clinical guideline was to produce the most

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Respiratory Nurse Specialists				a number of issues and concerns relating to the practicalities and service implementation of the recommendations, which we feel NICE, should take in to consideration, before publication. We believe the highlighted concerns would have an impact on, the workload in both primary and secondary care, may potentially add to confusion and could result in uncertainty and misunderstanding around asthma care best practice. We would be extremely grateful if the concerns of our members could therefore be taken in to account.	clinically and cost effective way to diagnose asthma accurately. The GDG acknowledges that the implementation of some objective tests in primary care will require initial investment and training. However, the health gains and improvements in patient outcomes have been shown to be clinically effective as well as cost effective for the NHS; please see the health economic analysis in appendix M. The NICE Implementation team will produce support materials to facilitate uptake of the guideline into clinical practice. Furthermore, the GDG do not consider that all of the recommendations are new to clinical practice, for example, spirometry services should be available in all GP practices already. The only new objective test recommended in the guideline is a FeNO test, however, the GDG consider that performing a FeNO test is much easier than performing spirometry. Furthermore, the view of the patient members of the GDG is that patients want certainty of diagnosis before being put on life-long treatment.
Association of Respiratory Nurse Specialists	Full	General	General	Spirometry • Performing spirometry for children from the age 5 will be a new area of practice across the	Thank you for your comment. The NICE Implementation team will produce support materials to facilitate uptake of the guideline into clinical practice.

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				UK and members have expressed concerns that there will be significant training issues for GP's and Practice Nurses. Training around spirometry in children isn't widely available, which increases the potential for misdiagnosis if the results are not good quality and reproducible. We therefore believe NICE should recognise this and work with relevant bodies to address this. • It has also been reported that the adult mouthpieces are too large for young children to use, so there will need to be some product development to enable this to be complied with. • Spirometry will only provide a clinical picture on that day. Members are concerned that using spiromety to diagnose may miss a diagnosis if the patient attends for the test on a day when their asthma is not causing symptoms, and the view of our members is that serial peak flows should feature more strongly within the	The GDG was aware that spirometry may not show airflow obstruction on any given day. The recommendations and algorithms indicate how to proceed in this event, and include the possibility of performing serial peak flow measurements. The GDG acknowledges that there is a paucity of diagnostic test accuracy data in children and hence made a high priority research recommendation to elucidate the best diagnostic pathway. The GDG has amended the recommendations for FeNO and BDR from 'offer' to 'consider' in children to reflect the evidence base. A footnote on the diagnostic cut-off values for children has also been added to the recommendations on spirometry and BDR. Furthermore, the GDG has added a caveat to the diagnostic algorithm for children to account for those children who are unable to perform objective tests from age 5 onwards that the principles in recommendation 1.2.1 should be followed until the child is old enough to perform objective tests adequately.

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				guidelines.	
Association of Respiratory Nurse Specialists	Full	General	General	FENO monitoring and Bronchial Challenging • Whilst there is research evidence supporting the use of FENO measurement, within clinical practice, widespread availability of machines is very low. Responses from our members have been that the cost of machines is seen as very prohibitive and without the availability of machines, a sudden reliability on secondary care will occur and referrals to secondary care would be a real risk. Some areas reporting a 30 week wait for referrals to secondary care and so this would be an increased and unnecessary burden on secondary care. • Outside of research centres and large tertiary centres, bronchial challenges are not widely available, so again the impact that this will create on time and purchasing of equipment	Thank you for your comment. The GDG acknowledges that FeNO testing in primary care is new and will require some initial investment. However, the best available evidence supports the clinical and cost effectiveness of FeNO and therefore the GDG considered the initial investment worthwhile for long-term patient health gains from increased accuracy in asthma diagnoses and reduced demand on NHS services, for example, preventable unscheduled healthcare utilisation. Currently bronchial challenge testing is available in secondary care but the GDG acknowledge that this service provision is not widespread. Hospitals with a lung function laboratory should be able to perform challenge tests. The GDG acknowledges that patients in some areas of the country may need to travel to undertake a bronchial challenge test. However, the evidence available to the GDG suggests that this is the best single test for asthma, and that making it more widely available would improve the diagnosis of asthma. They also noted that the test is widely used in other countries, and

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				will be significant. • Without a strong argument from NICE, which clearly demonstrates the improvement in asthma care that these 2 tests provide, we believe there is a real risk that these recommendations will be ignored in clinical practice.	felt that the UK lags behind in this regard. The current coverage is unknown however if there is more demand in future this service provision will become more widely available. Please see chapters 16 and 18 respectively for the clinical and cost effectiveness evidence for FeNO and bronchial challenge testing, as well as the cost effectiveness analysis in appendix M.
Association of Respiratory Nurse Specialists	Full	General	General	Clinical Time • Asthma patients in primary care clinical practices have a 10 or 15 min appointment, with the practice nurse. Increasing testing and the range of investigations, required to make a diagnosis, would therefore create a requirement for more lengthy appointments and increased pressure that this inevitably creates needs to considered.	Thank you for your comment. The time taken to perform a spirometry was based on expert consensus. In the model a sensitivity analysis was conducted if the time used to perform the test is doubled to 30 minutes then the use of spirometry remains cost-effective. Time, and other resources, are wasted by incorrect diagnosis, and a major aim of this guideline is to reduce this wastage. Resources saved through reducing wastage could perhaps be reinvested to relieve pressure on services.
Association	Full	Gener	General	Guideline Confusion	Thank you for your comment. NICE has met with

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of Respiratory Nurse Specialists		al		• Clinicians in practice currently refer to the BTS/SIGN guidelines (2014). We feel the publication of the NICE guidelines, which offer different advice, will add to confusion in clinical practice. We therefore feel there needs to be a far better communication and collaboration with professional organisations; to ensure confusion and over production of guidelines doesn't occur.	both BTS and SIGN to discuss the current guideline, and potential future asthma guidance.
Association of Respiratory Nurse Specialists	Full	General	General	Positive Aspects of Guidelines • Several members have responded positively to having Asthma Control Test within the guideline as it is easy to use and very accessible. Members were also encouraged by the recommendations regarding inhaler technique.	Thank you for your comment.
Association of	Full	General	General	In summary ARNS believes that if there is strong evidence base to support a fundamental shift in	Thank you for your comment. The aim of NICE clinical guidelines is to provide evidence-based

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Respiratory Nurse Specialists				clinical practice, which will affect both primary and secondary care, NICE should provide an achievable timeline to allow the supporting infrastructure to be developed. We believe that in order for the guidelines to be implemented within clinical practice, clinicians will need the support of a number of respiratory organisations. We would therefore welcome a meeting with you to potentially work together, to ensure that we are able to support the rationale behind the guidelines, and negotiate a practical timeline for implementation of the recommendations within clinical practice.	guidance on improving health and patient care and cost effectiveness to the NHS. NICE clinical guidelines are not mandatory and there is no definitive time pressure for implementation.
Asthma UK	Full	General	General	We welcome NICE's continued work to improve the quality of asthma care through clinical guidelines and standards, and welcome the opportunity this guideline will present to improve the lives of people with asthma. The most important factor to consider when developing a diagnosis and monitoring guideline is that people with asthma receive the timely diagnosis and treatment they need as early as possible, and that their condition is	Thank you for your comment.

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				effectively monitored throughout their life to ensure that they receive the right treatment at the right time to reduce their risk of asthma attacks.	
Asthma UK	Full	General	General	Overall, we welcome the attempt to capture the best research available and translate this into a more systematic approach to the asthma diagnostic process. Over the next five to ten years, we should see advances in this area and this guideline is a good start until more evidence and tests are identified. However, although this guideline takes us some way to improving the asthma diagnosis pathway, it is clear that the evidence remains limited and that **there is still no definitive diagnostic test(s): even when using this 'gold standard' approach it will still not be possible to confirm someone definitely has, or does not have, asthma due to its variability, especially in relation to seasonal triggers such as pollen and colds.** The impact of a complex, lengthy diagnostic process on people with asthma must therefore be considered in light of the fact that a definitive diagnosis of asthma will still not be possible because the condition may change throughout the seasons or indeed throughout someone's life. **Patients must be fully aware of the limitations of the diagnostic tests which only reflect symptoms at one point in time**	Thank you for your comment. The diagnostic accuracy of the algorithm is based on the best available evidence and aims to provide the most clinically and cost effective way to diagnose asthma. Whilst the GDG acknowledges that there is no single test or set of tests to 100% definitively diagnose asthma, the diagnostic algorithm the GDG has produced provides the highest level of confidence of an asthma diagnosis, or of a non-asthma diagnosis. The algorithm also provides room for people with 'suspected asthma' for their diagnosis to be reviewed which will allow other diagnoses to be considered. We agree that the process of monitoring, properly conducted, can either cement or call into question, the diagnosis of asthma. However, there is no formal evidence which allows recommendations on this; it relies on the experience of healthcare professionals and patient-dependent factors. We also agree that the monitoring process can be used to refine aspects of asthma management, but again it is hard to capture this in generalisable evidence-based

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				and do not reflect variability such as seasonality. **The monitoring aspect of the guideline should therefore be considered as an integral part of diagnosis**, until more diagnostic evidence is available. **Continuous monitoring after initial diagnosis, and then later through an annual asthma review, presents the only effective way of confirming diagnosis throughout the seasons, collecting a body of evidence to understand more about a person's asthma so that they only take asthma medication when they need it.** Such initial monitoring must then be followed up with a 'world class' annual asthma review to monitor ongoing symptoms, control, triggers and adherence. This is especially the case for children and young people, or elderly people, whose symptoms may be more likely to change over the long term, putting them at higher risk of an asthma attack. The guideline should therefore reflect the significance of monitoring in enhancing diagnosis and contributing to risk reduction, more than it currently does**.** **The guidance should also not prevent reviews from being delivered more dynamically, against the desire and needs of both patients and health care professionals (for example, using informatics to**	recommendations. Regarding the use of telehealthcare, the evidence was not sufficiently strong for the GDG to make a national recommendation in support of the use of telehealthcare to monitor asthma control; please see chapter 30 for the clinical and cost effectiveness evidence. However, the GDG made a future research recommendation to investigate the clinical and cost effectiveness of telehealthcare. The guideline recommendation does not prohibit use of telehealthcare (the GDG did not make a 'Do not' recommendation) if healthcare providers wish to make the capital investments in telehealthcare systems.

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				transmit monitoring information remotely, communicating with patients via telephone and video conferencing). If specific tests must be performed at each review, regardless of whether patients are at low or high risk, then this could be a potential barrier to a digital shift in care. To reduce risk of asthma attacks, monitoring should also be focused towards identifying those patients who are at highest risk (for example, children, those who smoke, those recently hospitalised, and those who over-use blue inhalers), and alternative mechanisms should be in place for those at lower risk and less engaged. Effective monitoring will result in better prevention of asthma attacks, in line with the vision described in the Five Year Forward View. In summary: • Although asthma diagnosis is important, the current diagnostic tests available will only ever provide a snap shot view of symptoms which will change throughout the seasons, for example during pollen or cold and flu seasons. • Patients must therefore be fully informed that there is no diagnostic process which can	

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				definitely diagnose asthma. • In this context, it is vital that initial monitoring is conducted as part of the broader diagnosis, to continually track symptoms, triggers, control and adherence, and that this monitoring then evolves into an appropriate annual asthma review. • Annual asthma reviews are currently not being delivered as frequently as they should be, and do not always include the right basic elements, despite incentives and national focus. As such, the challenges of implementing a new diagnostic pathway with new tests and equipment should not be underestimated. When identifying priority areas for implementation, emphasis should firstly be placed on effective monitoring. Only secondly should it be placed on confirming diagnosis, and only then in those who asthma may vary most: children and young people in the first instance. • The monitoring process should not be designed in a way which prohibits a more dynamic, digital approach to monitoring and reviews using technology.	

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Asthma UK	Full	General - Diagnosis	General - Diagnosis	The importance of balancing the specificity of tests (identifying those who don't have asthma), and sensitivity (identifying those who do) is well articulated. However, due to the repeated emphasis on an estimated over diagnosis of asthma which was cited in the scope, there is a risk that the approach cited may be biased towards specificity, leading to premature exclusions of asthma which could put patients at risk. Over-diagnosis is frequently referenced in the documents (for example, Full Guideline, pp. 25, 27, 51, 164 etc.). However, there is no reference to the methodology used to come to this conclusion and how the 30% over diagnosis figure was taken as the most important factor in diagnosis (in contrast to other papers which cite under diagnosis). For example, calculations in the Full Guideline are made on direct bronchial challenge testing on p. 164 using a figure from one paper (Aaron et al), which estimated that a third of people currently diagnosed are misdiagnosed (of which a 35% had to seek help for their asthma or had to restart asthma medication in a six month follow up period). It is unclear why this paper alone was used to complete this calculation and why over diagnosis was considered a priority above the risks associated with under diagnosis.	Thank you for your comment. We agree that there was an unintentional and misleading emphasis on over-diagnosis in the guideline 'linking evidence to recommendations (LETR)' section and have now added the importance of under-diagnosis to the LETRs and guideline introduction. We would like to clarify that the GDG did not bias towards specificity. The GDG acknowledges fully that over-diagnosis AND under-diagnosis is a problem, as shown by published literature. The primary aim of this guideline was to produce the most clinically and cost effective way to accurately diagnose asthma in people who do have asthma and to rule out asthma in people who do not have asthma. The sensitivities and specificities of objective tests reviewed were taken fully into consideration with this aim. The diagnostic algorithms are not biased towards ruling asthma out in people who have the possibility of having asthma. Regarding the 30% over-diagnosis figure, further evidence has now been cited. For the statement "almost a third (30%) of adults do not have clear evidence of asthma" the guideline development group is aware of consistent evidence and cross-

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				As such, the guideline may overlook the wealth of evidence which suggests that there is also a significant problem of under diagnosis in asthma (for example, within various different groups including children, adolescents and the elderly). There is a risk that in the recommended approach, normal results could lead to a misplaced decision to exclude asthma: just because all of the test results are normal it does not mean that someone does not have asthma.	sectional surveys (5 references are given below) that suggest a large proportion of people treated for asthma at a single point in time do not have objective supportive evidence, or had normal objective tests. This is not to say that they were all misdiagnosed. The other possibilities are that their treatment has been so effective as to make all objective findings normal (in which case stepped-down treatment should be considered), or that spontaneous changes in an intrinsically variable condition have meant that, at that moment in time, all objective findings were normal. Without incidence studies with tests done at the time of presentation and diagnosis, the true figure is unknown. The GDG accepts that over-diagnosis has been emphasised in the write-up more than under-diagnosis, and that both are important. Both were considered equally when reviewing the evidence, and the guideline has been amended to reflect this. 1. Starren ES, Roberts NJ, Tahir M, O'Byrne L, Haffenden R, Patel IS, Partridge MR. A centralised respiratory diagnostic service for primary care: a 4-

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					year audit<http://www.ncbi.nlm.nih.gov/pubmed/22430040>. Prim Care Respir J 2012; 21(2): 180-186 2. Linden Smith J, Morrison D, Deveau C, Hernandez P. Overdiagnosis of asthma in the community<http://www.ncbi.nlm.nih.gov/pubmed/15045041>. Can Respir J 2004;11(2):111-16. 3. Aaron SD, Vandemheen KL, Boulet LP, et al. Overdiagnosis of asthma in obese and nonobese adults<http://www.ncbi.nlm.nih.gov/pubmed/19015563>. CMAJ 2008;179(11):1121-31. 4. Marklund B, Tunsater A, Bengtsson C. How often is the diagnosis bronchial asthma correct<http://fampra.oxfordjournals.org/content/16/2/112>? Fam Pract 1999;16(2):112-16. 5. Shaw D, Green R, Berry M, Mellor S, Hargadon B, Shelley M, McKenna S, Thomas M, Pavord I. A cross-sectional study of patterns of airway dysfunction, symptoms and morbidity in primary care asthma http://www.ncbi.nlm.nih.gov/pubmed/22786814 Prim Care Respir J. 2012 Sep;21(3):283-7. doi: 10.4104/pcrj.2012.00057
Asthma UK	Full	General - Diagn	General - Diagnos	The algorithms for diagnosing asthma are very helpful, however, they could include further considerations about the impact on the patient in the following ways:	Thank you for your comment. NICE produces an 'information for the public' version of the recommendations. We will refer these points to

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		osis	is	• Comprehension: most importantly, patients should be informed that it is not possible to get a definitive diagnosis of asthma using current tests available. Patients should also be informed and able to understand which tests are being performed and why. All patients should be informed as to why some distressing tests are being performed and also understand why they may not be able to perform all of the manoeuvres required. • Partnership approach: consideration should be given as to whether it is reasonable to expect patients to attend multiple appointments at multiple locations for multiple tests. Impact on travel, costs, and time out from work / school must be considered, as well as the fact that a definitive diagnosis may still not be reached. A discussion should be had with the patient to understand their needs. • Are there risks associated with a single patient having multiple tests performed by multiple professionals, at different locations, with potentially with varying levels of skills? Inconsistencies and errors may occur and	NICE for consideration when finalising this version of the guideline. In terms of multiple attendances for testing, the GDG was supportive of more tests if it increased the likelihood of an accurate diagnosis. The time taken to attend testing is fully justified if it reduces the risk of missed diagnoses and risk of severe exacerbation which you previously state is a major problem in people who are un-diagnosed with asthma. The GDG felt that the diagnostic algorithm could be completed with a minimal number of attendances relative to current practice which would require the individual to have just as many attendances to review a trial of treatment for example. Therefore even though costs to the patient have not been explicitly incorporated in the economic model, as NICE methodology only considers costs that fall on the NHS, the difference in these costs between current practice and what is recommended will be marginal. Finally there was a strong preference from patient representatives on the guideline to undergo further diagnostic testing if it meant reducing the risk of misdiagnosis. Healthcare provision for other conditions may well

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				considerations should be given to the value of having consistent testing performed, and access and availability of trained staff should be considered. • What is the risk to patients in delaying treatment until a diagnosis is confirmed if the diagnostic process takes a long time? The guidelines must be clear in stating that treatment should commence and continue as a way to reduce the risk of asthma attacks, even when diagnosis remains unclear. Treatment itself is a valuable part of the diagnostic process in that it is possible to trial treatments and assess response. • In light of all of the above, the term 'consider' rather than 'offer' should be used for all diagnostic testing recommendation. • Refer to the development of a written asthma action plan once diagnosis is 'confirmed'.	be delivered by a team of healthcare professionals, for example, diagnostic testing for heart failure, and there is no reason why asthma should be atypical in this regard. In addition, service provision and training needs are outside the remit of this guideline. The GDG agrees that treatment should not be delayed in people who are acutely unwell and has added three recommendations at the start of the guideline to make this clear. Trials of treatment are certainly used traditionally, but there is little formal evidence to support their use. Regarding your point about the term 'consider', the strength of the recommendations is based on the GDG's review of the best available evidence. The term "consider" is indeed used more than "offer", reflecting the concerns to which you allude, but in a small number of instances the GDG felt that evidence was strong enough to use "offer". Personal Asthma Action Plans are outside the scope of this guideline and therefore the GDG cannot make any recommendations on these. Regardless,

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					the role of PAAPs is covered in the NICE quality standard on asthma and will be considered for inclusion in the forthcoming NICE Guideline on Asthma Management.
Asthma UK	Full	General - diagnosis	General - diagnosis	As mentioned in the scope, the diagnosis aspect of the guideline relates to patients who are currently being investigated for suspected asthma. However, this could easily be overlooked within the document resulting in two adverse effects. Firstly, that patients with asthma are unfairly scrutinised and made to feel deceptive because they may not currently be experiencing symptoms (either due to good symptom control or an absence of triggers). Secondly, precious resources could be spent investigating existing patients when their asthma has already been diagnosed. This guideline should not instigate a review of every single asthma patient's diagnosis, and the documents should be more explicit in this regard. People with asthma are often telling us about their experience when their diagnosis is questioned. One person told us: "I once had a doctor tell me I didn't have asthma (I was diagnosed at 2 and this incident was when I was about 17) he stopped all my inhalers and told me I would be fine...2 days later I was rushed to hospital with a severe attack".	Thank you for your comment. Nowhere does the guideline say that a review should be instigated of every asthma patient's diagnosis. As you state, the diagnosis recommendations are for people under investigation for suspected asthma, not people with a diagnosis of asthma. We have added a sentence to the guideline introductions to clarify this.

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Asthma UK	Full	General - diagnosis	General - diagnosis	The algorithms are very helpful but may also be considered complex. The logic behind how each test was prioritised and ordered could be clearer, and the value of each test in isolation is overlooked. For example, if clinicians only have access to some tests, or a patient only wants to go for one or two tests, it is difficult to know how a clinician would prioritise tests. Consideration should also be given as to how quality assurance will be given as to the quality of testing being performed. There is potential risk to patients if an unknowingly incompetent healthcare professional revoke diagnosis of asthma and removes treatment due to negative results, leading to the patient having an asthma attack.	Thank you for your comment. Because no test is perfect (as per your earlier comment) the GDG has attempted to increase accuracy by suggesting more than one. Inevitably this involves some increase in complexity. We acknowledge that patients and their doctor may, in an individual case, not wish to undergo all the recommended tests, but the risk of suggesting within the guideline which tests should be prioritised is that the other tests will be regarded as easily dispensable. Please refer to section M.2.1.1 in the health economic analysis in appendix M which provides all the detail around how each test was positioned in the diagnostic pathway. The placement of each test in the diagnostic algorithm is also discussed in each of the test's economic considerations section in the LETR. Guidance on quality assurance of testing is outside the remit of this guideline and is available from other sources.
Asthma UK	Full	General	General - diagnosis	We were surprised that diagnosis through trial of medication was not considered as a potential method for diagnosis as this issue can be contentious and a review of the evidence would be helpful. It is currently	Thank you for your comment. The GDG disagrees that trial of treatment should be given on the basis of symptoms alone. Trials of treatment are certainly used traditionally, but there is little formal evidence

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				recognised as one of the more common diagnostic techniques practiced. For example, in a survey we conducted on GPs and Practice Nurses in 2015, 67% said they currently use this method to diagnose asthma. However, we are aware that the evidence in this area is limited and an evaluation would be very useful. This especially the case for children who may be unable to complete diagnostic tests: it is vitally important that parents understand that diagnosis is not definitive and are aware of the importance of adherence within this context.	to support their use. We note that BTS/SIGN also found no good trial evidence and that the use of a trial of treatment is graded as a Good Practice Point for children and a Grade C recommendation for adults within that Guideline. A contra-view is that they can lead to misdiagnosis when a natural improvement in symptoms coincides with, and is spuriously attributed to, introduction of asthma therapy. The proposed diagnostic sequence allows their use in cases of genuine doubt (see algorithms B1 & C) but encourages the use of more objective tests beforehand. The diagnostic endpoints do factor in reviewing the diagnosis of asthma based on response to treatment.
Asthma UK	Full	General	General - monitoring	People with asthma and health care professionals both tell us that the traditional asthma review model will need to evolve in order to be fit for purpose for all people with asthma, for example, using apps, and telephone / video communications. By recommending that spirometry and / or peak flow monitoring should occur at each review, the guideline may limit the potential for asthma reviews to occur more remotely for those who are at lower risk, and less engaged.	Thank you for your comment. Regarding the efficacy of telehealthcare, the best available evidence does not currently support its use for monitoring asthma control for the GDG to make a national recommendation advocating its efficacy. The GDG made a future research recommendation. The guideline does not preclude its use (the GDG did not make a 'Do not' recommendation) if healthcare providers wish to make the capital investments in telehealthcare systems.

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Asthma UK	Full	51	8-12	We welcome the acknowledgement that asthma is complex and highly variable, as this is what makes it so much harder to diagnose than other lung conditions. However, it would be helpful to see this reiterated more frequently and clearly throughout the documents, in conjunction with the fact that no single or group of tests can either confirm or disprove asthma diagnosis.	Thank you for your comment. We appreciate that these are important points; they are stated within the guideline.
Asthma UK	Full	84-85	Box 10.6	The guideline recommends that occupational asthma should be checked in those newly diagnosed and in those with established asthma which is poorly controlled. This recommendation should be referred to in the monitoring section in addition to, or instead of, the diagnosis section. It may also be helpful to note incident airway disease in these sections also.	Thank you for your comment. We agree and have added 'and if relevant ask about occupational and or other triggers' to recommendation 1.3.1 'Monitor asthma control at every review…'.
Asthma UK	Full	103	Quality of Evidence	We were interested to note the inclusion of BDR and while we welcome it, believe that more detail could emphasise the importance of taking the time to conduct the test properly to ensure patients are not put at risk.	Thank you for your comment. Specific instruction on the proper administration of tests is outside the remit of this guideline. This guidance is available from other sources. For example, spirometry standards are given by the ARTP. We state clearly in the LETR that the diagnostic accuracy of the algorithm is dependent on the correct administration of the objective tests.
Asthma UK	Full	110-111	Entire box	Due to the fact that peak flow variability offers the potential to track lung function over time, is simple, and non-invasive for patients, we were surprised to see it	Thank you for your comment. The clinical evidence on the sensitivity and specificity of PEFv is taken fully into account by its position in the diagnostic

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				lower down in the algorithm. As the only test which can offer more than a single snapshot of lung function, addressing potential seasonal variability, it can be very helpful in diagnosing asthma when conducted sequentially by an engaged and appropriately trained patient. Its value as an accessible, cost effective, comfortable test for people with asthma (rather than a rule in test) should not be overlooked without proper consideration.	pathway. The evidence shows that PEF variability is an insensitive test for asthma (please see chapter 13 for the clinical and cost effectiveness evidence on the diagnostic test accuracy of PEFv) meaning that the vast majority of individuals with asthma would receive a negative result from this test. The GDG felt that due to this an individual with asthma could receive a faster diagnosis with the use of other objective tests, on top of the fact that peak flow monitoring also takes between 2 – 4 weeks.
Asthma UK	Full	142-143	Other considerations	As FeNO levels can be altered by smoking, previous smoking history, diet and oral CS, this should be addressed in both the recommendation and the algorithms.	Thank you for your comment. We agree that because the FeNO test can be affected by smoking status we have added a recommendation to reflect this. The prevalence of smoking in people with asthma is approximately 20% meaning that cigarette smoke will not affect the diagnostic accuracy of FeNO in 4 out of 5 people. This is a diagnostic guideline and smoking cessation is outside the remit of this guideline. The OCS evidence on FeNO is ambiguous. People on OCS stop their ICS which may have an impact on FeNO.
Asthma UK	Full	212-213	Box	It would be helpful to specify that spirometry only ever provides a single snapshot view and that even if spirometry results remain consistent across reviews, it	Thank you for your comment. Please refer to recommendation 1.2.2 which states that the diagnosis of asthma should not be made on the

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				does not eliminate the possibility that asthma symptoms are present at other times. There are also challenges in terms of availability of the correct equipment for children and young people in primary care settings, in addition to the quality of training which makes its implementation challenging. Spirometry services run by an appropriately trained staff (as opposed to spirometry/spirometers) should be referred to as a potentially successful model of delivery to address accessibility and training concerns to ensure the person performing the tests and interpreting the result is adequately trained. This may help to address access and training challenges. As mentioned above, if spirometry is mandatory at each review, this could limit the potential for ongoing monitoring and reviews to be delivered more dynamically, using digital technology.	basis of any single test alone. The GDG acknowledge that the implementation of some objective tests in primary care will require initial investment and training. The NICE Implementation team will produce support materials to facilitate uptake of the guideline into clinical practice. Furthermore, the GDG does not consider that all of the recommendations are new to clinical practice, for example, spirometry services should be available in all GP practices already. NICE clinical guidelines are not mandatory. For your point regarding monitoring by digital technology, please refer to chapter 30 for the clinical and cost effectiveness evidence of telehealthcare to monitor asthma control.
Asthma UK	Full	227, 233	Boxes	We welcome the use of FeNO as a test for monitoring inflammation, as this could provide an indication of adherence, which is an extremely important area to address as early as possible.	Thank you for your comment.
Asthma UK	Full	252-5	Box	We welcome the high priority research recommendation on adherence monitoring mechanisms.	Thank you for your comment.
Asthma UK	Full	263	Box	We welcome the emphasis placed on the importance of	Thank you for your comment. A comparison of

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				checking inhaler technique, and would also like reference made about the positive value of spacers.	different inhalers which includes the addition of spacers to an MDI is outside the scope of this guideline.
Asthma UK	NICE	General	General	In recommendation 1.1.3 it is stated that 'even if examination results are normal the person may still have asthma'. This should be reiterated for each of the recommendations which refer to specific diagnostic tests.	Thank you for your comment. The recommendations are not intended to be read in isolation therefore it is not accurate to apply this statement to every recommendation. The diagnostic pathway provides the sequence of tests that should be conducted based on the results of the preceding test. The GDG reviewed the sensitivities and specificities of all the objective tests under consideration and deemed that if a person tests negative for obstructive spirometry, negative FeNO, no peak flow variability they most likely do not have asthma.
Asthma UK	NICE	General	General	Where peak flow variability is mentioned, this should be defined as one or more spikes or dips in readings with specific values and variations.	Thank you for your comment. Peak flow variability is explained in the clinical introduction of chapter 13.
Asthma UK	NICE	General	General	Reference should be made somewhere to indicate that treatment should be initiated, even prior to diagnosis (or all diagnostic tests in the algorithm being completed). It would pose a significant risk to patients if treatment was withheld until all tests are completed, as this could take some time and the symptoms would still persist, putting patients at risk of an asthma attack.	Thank you for your comment. The GDG agrees that no patient who is acutely unwell should have a delay in getting treatment for their symptoms and therefore the GDG has added three recommendations at the start of the guideline to make this clear.
Asthma UK	NICE	Gener	General	We were surprised that no reference is made to creating	Thank you for your comment. Personal Asthma

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		al		and amending written asthma action plans within both the diagnosis and the monitoring sections as there is substantial evidence for their effectiveness.	Action Plans are outside scope of this guideline as this falls under asthma management (self-management) and therefore the GDG could not make any recommendations on PAAPs.
Asthma UK	NICE	3	Introduction, Para. 1	The introduction should explicitly state the variable nature of asthma and that it can change throughout someone's life, throughout the year and from day to day.	Thank you for your comment. We have made this change.
Asthma UK	NICE	3	Introduction, Para. 2	Can you please confirm the source of the statistic, 'in the UK, 4.1million people get treatment for asthma': according to our latest figures this is nearer 5.4 million.	Thank you for your comment. This figure is now cited.
Asthma UK	NICE	3	Introduction, Para. 3	In this section, it should be acknowledged that under diagnosis exists in addition to over diagnosis. It is irresponsible to focus only on over diagnosis as it may put patients at risk.	Thank you for your comment. This change has been made.
Asthma UK	NICE	3	Introduction, general	This section should place an emphasis on the fact that there is not enough research completed to identify a definitive test for asthma due to its variable nature, and that monitoring is the most effective way to confirm that a person is on the correct medication at the correct time. Asthma diagnostic tests simply indicate that monitoring should commence, rather than confirming that asthma is present. This should also be reflected on p. 4.	Thank you for your comment. We believe that following the suggested diagnostic process will lead to more certainty at an earlier stage than is currently the case. However, we agree that in some cases there will still be doubt and that a period of treatment, monitoring and re-testing will be necessary; the guideline includes this possible scenario.
Asthma UK	NICE	4		It should be emphasised that while diagnostic tests are	Thank you for your comment. We have removed the

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				important for those being newly diagnosed with asthma, monitoring is highly important for the 5.4 million people in the UK who are already being treated with asthma as a way to identify and reduce risk of asthma attacks, and to ensure they are on the correct medication when they need it. Both diagnosis and monitoring should be noted as a means of identifying high risk patients and reducing exposure to unnecessary and expensive treatments in order to step up or step down treatment as required. The second paragraph from the bottom should be amended to either reflect that other aspects of management were excluded because a new guideline is in development which will address this, or because diagnosis and monitoring is seen as the first priority. Reference to over diagnosis should be removed as it implies that management is not important, and suggests that it is more important to identify people who do not have asthma than to treat those who do effectively.	words "This is because there is evidence that incorrect diagnosis is a significant problem" from page 4 of the NICE version and the full guideline introductions. The GDG considers that the rest of the guideline introduction captures the issues around diagnosis and monitoring of asthma perfectly reasonably and sufficiently.
Asthma UK	NICE	5	Patient-centred care	It should be noted that the ability of patients to make informed decisions about their care is especially important for asthma, where several complex and intrusive tests may be offered which may still not result in a definitive diagnosis of asthma. They must aware that, even after completing all of the tests, their diagnosis may change throughout the seasons or years.	Thank you for your comment. The primary aim of this clinical guideline was to produce the most clinically and cost effective way to diagnose asthma accurately. The objective tests recommended are easy to perform and are non-invasive. NICE produces an 'information for the public' version of the recommendations. We will refer these points to

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				In the last paragraph, the final sentence should be revised to say 'Monitoring and management should be reviewed' for two reasons: firstly, because if monitoring is completed successfully then the right treatment will be provided at the right time to the right people in the right way (diagnosis decisions will therefore not be relevant), and secondly because it may initiate a repeat of diagnostic tests at the transition stage which may not be clinically necessary, may be distressing for the patient, and may not be cost effective.	NICE for consideration when finalising this version of the guideline. The section on patient-centred care is standard text in the NICE version of the guideline and the importance of monitoring is captured in section 1.3 'Monitoring asthma control'. The GDG disagrees with the point about 'diagnosis decisions will therefore not be relevant'. The GDG were very supportive of having additional tests if these are helpful in obtaining a confirmed diagnosis of asthma before being put on prolonged treatment.
Asthma UK	NICE	14	Recommendations	1.1.1 Should include 'tight chest', and should state that only one, some, or all, of these symptoms may be present. It should be stated somewhere that (as in 1.1.2), one should not use an objective test alone to diagnose asthma. A reference could also be made to evaluating through trial of medication, and how to assess response.	Thank you for your comment. The majority of the evidence reviewed did not include 'tight chest' as a symptom suggestive of asthma. The GDG does not consider that asking about a history of 'chest tightness' has utility in the diagnosis of asthma because it is not a symptom specific to respiratory disease and could be associated with multiple diseases, for example, heart disease. Please refer to recommendation 1.2.2 which states that asthma should not be diagnosed on the basis of any single test alone.

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					The GDG disagrees that trial of treatment should be given on the basis of symptoms alone. Trials of treatment are certainly used traditionally, but there is little formal evidence to support their use. We note that BTS/SIGN also found no good trial evidence and that the use of a trial of treatment is graded as a Good Practice Point for children and a Grade C recommendation for adults within that Guideline. A contra-view is that they can lead to misdiagnosis when a natural improvement in symptoms coincides with, and is spuriously attributed to, introduction of asthma therapy. The proposed diagnostic sequence allows their use in cases of genuine doubt (see algorithms B1 & C) but encourages the use of more objective tests beforehand. However, the diagnostic accuracy of 'trial of treatment' is outside scope and therefore not considered in the evidence reviews as a diagnostic test. The diagnostic endpoints do factor in reviewing the diagnosis of asthma based on response to treatment.
Asthma UK	NICE	17	1.1.9	'Offer' should be changed to 'consider' due to the distressing nature of a bronchial challenge test with histamine or methacholine, the risk this test may pose to	Thank you for your comment. The use of 'offer' vs. 'consider' in the recommendations is based on the strength of the evidence which underpins the

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				patients and the demands on the patients in travelling to receive this test in secondary care, as in 1.1.9.	recommendation. The evidence indicated that a challenge test is the best single test for the diagnosis of asthma, and therefore the GDG felt that "offer" was the correct term to use, The concerns that you express were debated by the GDG, and they form part of the reason why challenge testing is further down the diagnostic pathway, to be used only when other tests fail to confirm or refute a diagnosis. In terms of demands on some patients in travelling to receive this test in secondary care, the GDG was supportive of more tests if it increased the likelihood of an accurate diagnosis. The time taken to attend testing is fully justified if it reduces the risk of missed diagnoses. Bronchial challenge tests involve a modest degree of bronchoconstriction and rarely produce "distressing" side-effects.
Asthma UK	NICE	18	1.2	Reference should be made to the fact that there is not enough evidence to suggest that a single test or combination of tests can definitively rule in or rule out asthma.	Thank you for your comment. Please refer to recommendation 1.2.2.
Asthma UK	NICE	21	1.3.3	Reference should be made to the fact that completing peak flow or spirometry tests for monitoring should not prevent the development of a digital approach to asthma monitoring and reviews.	Thank you for your comment. The evidence was not sufficiently strong for the GDG to make a national recommendation in support of the use of telehealthcare to monitor asthma control; please see chapter 30 for the clinical and cost effectiveness

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					evidence. However, the GDG made a future research recommendation to investigate the clinical and cost effectiveness of telehealthcare. The guideline recommendation does not prohibit use of telehealthcare (the GDG did not make a 'Do not' recommendation) if healthcare providers wish to make the capital investments in telehealthcare systems.
Asthma UK	NICE	21-22	1.3.7	Add other scenarios: 'when requested by the patient', 'when poor adherence is suspected' and 'when a new device is provided'. Reference should also be made to the fact that adherence should be constantly reviewed, even if the guideline is not able to recommend specific tests.	Thank you for your comment. The GDG agrees that inhaler technique should be checked when there is deterioration in asthma control, and when requested by the patient, and has added these bullet points to the recommendation. Recommendation 1.3.7 already clearly states 'when the device is changed'.
Astrazeneca	Full	General	General	Severe asthma is not within the remit of this guideline; AstraZeneca would look forward to equivalent diagnosis and monitoring guidelines for this important patient group.	Thank you for your comment.
Astrazeneca	Full	261	28	We welcome the recommendations outlined in section 29.6, Recommendation 40 on monitoring inhaler technique, because this is important for improving patient outcomes. However we ask that further details be provided around this recommendation, in order to provide more clarity to healthcare professionals and avoid any unnecessary misuse in inhaler technique. Asthma sufferers who are unable to use their inhaler	Thank you for your comment. Please refer to chapter 29 on monitoring inhaler technique. The GDG agrees that correct inhaler usage is important. The best available evidence did not support a recommendation on best method for checking inhaler technique and hence the high priority research recommendation.

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				correctly are at increased risk of poor asthma control, potentially resulting in an exacerbation.[1,2] We believe that improved monitoring of inhaler technique is linked to better adherence of device, which itself is linked to better asthma control. In the 2014 NRAD report, it was found that of 195 asthma deaths, 48% were potentially linked to poor device adherence. Ensuring that patients receive appropriate training and are comfortable using the device before the inhaler is given to them will reduce misuse of the device,[2] contributing to better device adherence and asthma control.[3] We therefore ask that the recommendation for monitoring inhaler technique when the device is changed is brought in line with the BTS/SIGN recommendation in section 5.1 of their asthma guidelines, which states 'Prescribe inhalers only after patients have received training in the use of the device and have demonstrated satisfactory technique.' In the absence of findings from the research recommendations ['**What is the current frequency and the current method being used to check the inhaler technique of people with asthma? What is the optimal frequency and the best method of checking inhaler technique to improve clinical outcomes for**	

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				people with asthma?'], we would ask the GDG to provide consensus recommendations in the final guideline specifying the frequency and method of checking inhaler technique. This would provide benefits in terms of patient safety and improve the ability of patients to manage their asthma. We are aware of switch programmes where patients are being given a new inhaler without any technique training, and we are therefore concerned that currently some asthma patients receive new or different inhaler devices without being trained in inhaler technique. With the growing availability of therapeutic options in different inhaler devices, we believe more detailed guidance on inhaler technique monitoring is particularly important. Consensus guidelines on this would give clear national guidance about the frequency and method of inhaler device technique monitoring, improving the management of asthma patients. References 1. Al-Jahdali H et al. Allergy, Asthma & Clinical Immunology 2013; 9:8 2. Melani AS et al. Respir Med 2012; 106(5):757 3. Giraud V, Allaert FA and Roche N. Respir Med 2011; 105(12): 1815-22.	
Astrazenec	Full	145		Asthma is a heterogenous disease. We believe that by	Thank you for your comment. The best available

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a				identifying the predominant inflammatory pathway, whether it be IL-5 or IL-13, this can lead to better choice later on in the disease and allow a asthma management plan to be agreed upon early in the diagnosis of asthma by all stakeholders including the patient. We agree with the statement that eosinophils shouldn't be used as a diagnostic test for asthma. However we believe peripheral blood eosinophils count have a role in determining the predominant inflammation pathway and therefore future treatment choice in uncontrolled or partly controlled asthma [1, 2, 3] References 1. Ortega H, Katz L, Hartley B, Yancey S. Blood eosinophil count is a useful biomarker to identify patients with severe eosinophilic asthma. 2013; 2. Castro M, Wenzel SE, Bleecker ER, et al. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. Lancet Respir Med 2014; published online Oct 9. http://dx.doi.org/10.1016/S2213-2600(14)70201-2; 3. Castro M, Mathur S et al. Reslizumab for Poorly Controlled, Eosinophilic Asthma. American Journal of Respiratory and Critical Care Medicine	evidence did not support use of peripheral blood eosinophil count in the initial diagnosis of asthma. The role of the eosinophil in determining treatment later on in a person's disease trajectory is beyond the scope of this guideline.

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				2011;184(10): pp. 1125-1132)	
Astrazeneca	Full	230	39	We are pleased to see that understanding the role FeNO has to play in understanding asthma control is a top priority for the GDG and we look forward to understanding how the GDG intends to plan the schedule of work to answer this important research question	Thank you for your comment. However, please note that it is outside the remit of the GDG to 'plan the schedule of work to answer this important research question'.
Astrazeneca	Full	201	34	Clarification is required whether ACT referred to includes FEV1 or PEF as inclusion of PEF is not as accurate as FEV1. Which version did the GDG discuss?	Thank you for your comment. The ACT is a 5-question questionnaire with no measure of lung function.
AstraZeneca UK Ltd]	Full	General	General	AstraZeneca UK Ltd would like to thank NICE for the opportunity to comment on the draft scope for the Asthma: diagnosis and monitoring of asthma in adults, children and young people NICE clinical guideline	Thank you for your comment.
Boehringer Ingelheim Ltd	Full	General	General	Boehringer Ingelheim UK Ltd appreciated the opportunity to review the draft NICE Asthma Diagnosis and Monitoring Guideline as a stakeholder in the draft consultation. We welcome a guideline aimed at determining an effective diagnosis and monitoring strategy for asthmatic patients. We have no further comments.	Thank you for your comment.
British Medical Association	Full	General		Asthma is one of the most common long term conditions in the UK. Cost effective diagnosis requires the majority of diagnosis to be made outside of secondary care. This is currently the	Thank you for your comment. The GDG acknowledges that FeNO testing in primary care is new and will require some initial investment. However, the best available evidence supports the

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				case, however there is reasonable concern that asthma is over diagnosed, with consequences to the patient, and society. Missing the correct diagnosis, along with unnecessary treatment can put a strain on NHS resources. We are concerned that the proposed NICE guideline would ensure that almost all diagnoses for Asthma would have to be undertaken in secondary care as FeNo testing is not a primary care investigation, and currently there are no proposals to resource general practice to undertake this testing.	clinical and cost effectiveness of FeNO and therefore the GDG considered the initial investment worthwhile for long-term patient health gains from increased accuracy in asthma diagnoses and reduced demand on NHS services, for example, preventable unscheduled healthcare utilisation. FeNO is an extremely simple test to perform and can be done in primary care.
British Medical Association	Full	General		We are concerned that NICE is proposing to publish guidance which contradicts most of the recommendations made by the joint British Thoracic Society/SIGN guidance on the diagnosis, monitoring and management of Asthma which was published in October 2014 (Available to read here: https://www.brit-thoracic.org.uk/guidelines-and-quality-standards/asthma-guideline/.	Thank you for your comment. We do not agree that this new guidance contradicts most of the recommendations in the BTS/SIGN guideline. There are some differences, and these can be accounted for by updated evidence (not all of the recommendations in the BTS/SIGN guideline were reviewed in the 2014 version).

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				We would recommend that NICE review this document, and adopt recommendations from this guidance.	
British Medical Association	NICE	General		The NICE recommendations for the diagnosis of asthma in children and adults are complex and lengthy. The algorithms are too complex to be used by GPs in routine practice.	Thank you for your comment. The primary aim of this clinical guideline was to produce the most clinically and cost effective way to accurately diagnose asthma based on the best available evidence. The GDG disagree that the implementation of the diagnostic algorithm is prohibitively complex. Patients who present to their GP with mild symptoms of asthma can perform spirometry, BDR and FeNO tests during initial follow-up appointment with the practice nurse to get a positive diagnosis of asthma. Of these tests, only FeNO (which can be done in 5 minutes or less) is not part of the existing BTS/SIGN guidance. A small proportion of patients with diagnostic uncertainty will go through the longer route in the diagnostic pathway in order to obtain further objective testing evidence of asthma.
British Medical	Full	General		The British Thoracic Society/SIGN guidance and the NICE guidelines both recommend spirometry	Thank you for your comment. The GDG agrees that there is no infallible test to diagnose asthma. The

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Association				as the best initial diagnostic test from the age of 5 years through adulthood. 'In children, as in adults, tests of airflow obstruction, airway responsiveness and airway inflammation may provide support for a diagnosis of asthma. However, normal results on testing, especially if performed when the child is asymptomatic, do not exclude a diagnosis of asthma. Abnormal results may be seen in children with other respiratory diseases. Measuring lung function in young children is difficult and requires techniques which are not widely available. Above five years of age, conventional lung function testing is possible in most children in most settings. This includes measures of airway obstruction (spirometry and peak flow), reversibility with bronchodilators, and airway hyper-responsiveness.The relationship between asthma symptoms and lung function tests including bronchodilator reversibility is complex. Asthma	guideline represents the most clinically and cost effective way to diagnose asthma.

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				severity classified by symptoms and use of medicines correlates poorly with single measurements of forced expiratory volume in one second (FEV1) and other spirometric indices: FEV1 is often normal in children with persistent asthma. Serial measures of peak flow variability and FEV1 show poor concordance with disease activity and do not reliably rule the diagnosis of asthma in or out. Measures of gas trapping (residual volume and the ratio of residual volume to total lung capacity, RV/TLC) may be superior to measurements of expiratory flow at detecting airways obstruction especially in asymptomatic children. A significant increase in FEV1 (>12% from baseline) or PEF after bronchodilator indicates reversible airflow obstruction and supports the diagnosis of asthma. It is also predictive of a good response to inhaled corticosteroids (ICS). However, an absent response to bronchodilators does not exclude asthma' (British Thoracic Society/ Scottish Intercollegiate Guidelines Network, *British*	

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				Guideline on the management of asthma, 2014, page 16)	
British Medical Association	Full	13	32,33	The NICE recommendations then diverge with the BTS/SIGN guidelines. The NICE guidelines stating that for all patients with suspected asthma, except for children under 5 years, require a FeNO assessment. We have concerns about FeNO assessments, as it is not yet validated for diagnosing asthma, The evidence against using FeNO for diagnosis is rated 2+ in the BTS/SIGN guidance. We are also concerned at the resources required, as the equipment required is expensive and absent in primary care, although becoming more available in secondary care. FeNO is a useful predictor of response to inhaled steroids, but both documents point out that this is not a diagnostic for asthma as other conditions	Thank you for your comment. Please see chapter 16 on the clinical and cost effectiveness evidence for FeNO as a diagnostic test for asthma. The evidence paragraph to which you refer was not updated in the 2014 BTS/SIGN guideline, and contains no references after 2006. The FeNO analysis in these studies was not done using current equipment. The NICE guideline provides a more up to date review of the FeNO evidence. It is possible that when BTS/SIGN undertake a formal review of diagnosis the recommendations may be more positive regarding FeNO for diagnosis. The GDG acknowledges that FeNO testing in primary care is new and will require some initial investment. However, the best available evidence supports the clinical and cost effectiveness of FeNO and therefore the GDG considered the initial investment worthwhile for long-term patient health gains from increased accuracy in asthma diagnoses and reduced demand on NHS services, for example,

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					preventable unscheduled healthcare utilisation. FeNO is an extremely simple test to perform and can be done in primary care.
British Medical Association	Full	214	25	FeNO may have a role in monitoring and managing asthma but currently there is insufficient evidence that it should be used for diagnosis. Both the BTS/SIGN and NICE guidelines propose referral into secondary care for more specialist diagnostic testing such as airway challenge where the clinical symptoms are suggestive of asthma but spirometry and reversibility are negative. This seems to be a reasonable approach.	Thank you for your comment. Please see chapter 16 on the clinical and cost effectiveness evidence for FeNO as a diagnostic test for asthma.
British Medical Association	Full	201		We are reassured, that to monitor asthma, both BTS/SIGN and NICE recommend using a validated symptom questionnaire, for example, the Asthma Control Questionnaire. There is strong evidence that the achieving good control of symptoms significantly reduces the risk of an acute asthma attack. Checking the inhaler technique at an annual review is also recommended by both sets of guidelines.	Thank you for your comment. The option of PEFv and spirometry are given in recommendation 36 'Monitor asthma control at each review in adults and children aged 5 years and over using either spirometry or peak flow variability'. This is to account for the possibility that some patients due to technique have a suboptimal ability to produce a peak flow. So doing spirometry in these people may be more representative. The recommendation gives people the choice as it was GDG consensus that

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				We have concerns that NICE recommends that Fev1 is performed at every review for children over 5 years old, and adults. BTS/SIGN are clear in stating that isolated Fev1 reading bear little correlation to asthma severity and control. 'Asthma severity classified by symptoms and use of medicines correlates poorly with single measurements of forced expiratory volume in one second (FEV1) and other spirometric indices: FEV1 is often normal in children with persistent asthma. Serial measures of peak flow variability and FEV1 show poor concordance with disease activity and do not reliably rule the diagnosis of asthma in or out' (British Thoracic Society/ Scottish Intercollegiate Guidelines Network, *British Guideline on the management of asthma*, 2014, page 16) FeNO may have a role in managing step down of corticosteroid therapy in future:	one form of lung function testing could not be recommended over the other to monitor asthma control. The key point of this recommendation is that it is important to know a person's best lung function in order to judge severity of any acute deterioration, and since lung function changes with age it needs to be checked occasionally so that each individual's "best" is reasonably up to date. The point about FeNO is covered in the NICE DAP.

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				'Raised FENO (>50 ppb in adults and >35 ppb in children) is predictive of a positive response to corticosteroids. The evidence that FENO can be used to guide corticosteroid treatment is mixed. Low FENO (<25 ppb in adults; <20 ppb in the under 12 year old range) may have a role in identifying patients who can step down corticosteroid treatment safely' British Thoracic Society/ Scottish Intercollegiate Guidelines Network, *British Guideline on the management of asthma*, 2014, page 36)	
British Paediatric Respiratory Society	Full	General	General	The BPRS has severe reservations over the document as it stands, and the confused and illogical conclusions drawn. There is concern that many of the conclusions appear to be direct extrapolation of adult data onto children and young persons, and that the limited data in children is over interpreted. Our comments are confined primarily to the diagnosis of those aged 5-16 years,	Thank you for your comment. The GDG acknowledges that there is a paucity of diagnostic test accuracy data in children and hence made a high priority research recommendation to elucidate the best diagnostic pathway. The GDG has amended the recommendations for FeNO and BDR from 'offer' to 'consider' in children to reflect the evidence base. A footnote on the diagnostic cut-off values for children has also been added to the

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				and we are broadly supportive of the statements that apply to children aged 5 years or younger. We have not commented on the sections that apply to those aged over 16 year and adults. We had responses from 15 members – an exceptionally large number that reflects the major concerns that members have about the document. The ambition to introduce objective testing into diagnosis and monitoring is laudable, and was broadly supported, but the end result is a pathway that is confused and heavily dependent on objective tests and is fatally flawed. The confusion is highlighted by the key research recommendation for diagnosing asthma in children aged 5-16 years old "What is the acceptability and diagnostic accuracy of objective tests that could be used to comprise a diagnostic pathway for asthma in children aged 5–16 years old". We believe that this question remains unanswered. Ultimately this document suggests wide ranging changes to asthma diagnosis and management in children without justification. We have major reservations of the practicality of placing these	recommendations on spirometry and BDR. Furthermore, the GDG has added a caveat to the diagnostic algorithm for children to account for those children who are unable to perform objective tests from age 5 onwards that the principles in recommendation 1.2.1 should be followed until the child is old enough to perform objective tests adequately. Regarding the 30% over-diagnosis figure, further evidence has now been cited. For the statement "almost a third (30%) of adults do not have clear evidence of asthma" the guideline development group is aware of consistent evidence and cross-sectional surveys (5 references are given below) that suggest a large proportion of people treated for asthma at a single point in time do not have objective supportive evidence, or had normal objective tests. This is not to say that they were all misdiagnosed. The other possibilities are that their treatment has been so effective as to make all objective findings normal (in which case stepped-down treatment should be considered), or that spontaneous changes in an intrinsically variable condition have meant that, at that moment in time, all objective findings were normal. Without incidence

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				recommendations into clinical practice and will we believe cause unnecessary confusion to patients and healthcare workers, cost to health care services and most importantly potential harm and distress to children. The document starts with the premise that up to 30% of adults do not have clear evidence of asthma, although the evidence for this does not appear to be referenced. It appears that the document is predicated on a need to distinguish asthma from COPD in adults, and is driven with the laudable aim of increasing the specificity of asthma diagnosis in adults. There is however no recognition that there may significant under diagnosis of asthma in children e.g. global ISAAC data (Thorax 2009), and unfortunately many of the steps in the algorithm to increase specificity are at the cost of sensitivity. The diagnostic algorithm ends up being very test driven.	studies with tests done at the time of presentation and diagnosis, the true figure is unknown. The GDG accepts that over-diagnosis has been emphasised in the write-up more than under-diagnosis, and that both are important. Both were considered equally when reviewing the evidence, and the guideline has been amended to reflect this. 1. Starren ES, Roberts NJ, Tahir M, O'Byrne L, Haffenden R, Patel IS, Partridge MR. A centralised respiratory diagnostic service for primary care: a 4-year audit<http://www.ncbi.nlm.nih.gov/pubmed/22430040>. Prim Care Respir J 2012; 21(2): 180-186 2. Linden Smith J, Morrison D, Deveau C, Hernandez P. Overdiagnosis of asthma in the community<http://www.ncbi.nlm.nih.gov/pubmed/15045041>. Can Respir J 2004;11(2):111-16. 3. Aaron SD, Vandemheen KL, Boulet LP, et al. Overdiagnosis of asthma in obese and nonobese adults<http://www.ncbi.nlm.nih.gov/pubmed/19015563>. CMAJ 2008;179(11):1121-31. 4. Marklund B, Tunsater A, Bengtsson C. How

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					often is the diagnosis bronchial asthma correct<http://fampra.oxfordjournals.org/content/16/2/112>? Fam Pract 1999;16(2):112-16. 5. Shaw D, Green R, Berry M, Mellor S, Hargadon B, Shelley M, McKenna S, Thomas M, Pavord I. A cross-sectional study of patterns of airway dysfunction, symptoms and morbidity in primary care asthma http://www.ncbi.nlm.nih.gov/pubmed/22786814 Prim Care Respir J. 2012 Sep;21(3):283-7. doi: 10.4104/pcrj.2012.00057
British Paediatric Respiratory Society	Full	25	1	<u>Diagnosis of asthma for the document</u> Asthma is a heterogenous condition or conditions, and the BPRS has sympathy and admiration for NICE in attempting to come up with a simple and testable diagnosic test(s) for asthma. Both NICE and SIGN/BTS acknowledge that there is no specific diagnostic test for asthma and that the diagnosis is based on a probabilistic approach. The document proposes that the diagnostic tests under investigation would be performed in people with suspected asthma presenting to their GP. The reference standard was defined as physician diagnosis of asthma based on symptoms plus an	Thank you for your comment. The GDG acknowledges that there is a paucity of diagnostic test accuracy data in children and hence made a high priority research recommendation to elucidate the best diagnostic pathway. The GDG has amended the recommendations for FeNO and BDR from 'offer' to 'consider' in children to reflect the evidence base. A footnote on the diagnostic cut-off values for children has also been added to the recommendations on spirometry and BDR. Furthermore, the GDG has added a caveat to the diagnostic algorithm for children to account for those children who are unable to perform objective tests from age 5 onwards that the principles in recommendation 1.2.1 should be followed until the

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				objective test: - peak flow variability (more than 20% variability); - bronchodilator reversibility (improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls); - bronchial hyper-reactivity (PC20 of histamine or methacholine of less than or equal to 8mg/ml) Apart from the concerns we have over the requirements for one of these 3 criteria to diagnose asthma, we have major reservations over the validity of each individually. Table 32 (page 107) clearly shows that peak flow variability has good specificity in adults but this is not the case for children. Reference 22 in the guideline shows that peak flow variability lacks precision for diagnosis (the ROC curve is a diagonal line from bottom left to top right). There is no evidence for the 12% bronchodilator responsiveness cut off in children – this is merely data being extrapolated from adults. The document itself (page 99, table 28) highlights the fact that there is no evidence for use of bronchodilator reversibility (vs physician diagnosis of asthma) in	child is old enough to perform objective tests adequately. The core of your comment is that evidence is less good in children than in adults, and we agree with this. However, when it was suggested during scoping that, for this very reason, the guideline should be confined to adults, the clear response was that children should not be excluded and that the GDG should make the most of the available evidence.

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				5-16 year olds. There are exactly the same reservations over the use of methacholine (table 54) or histamine (table 55) page 156 challenge in children, with these deficiencies again highlighted in the document. It is clearly illogical that the document demonstrates that all 3 of the a priori asthma diagnostic criteria are not useful in diagnosing asthma.	
British Paediatric Respiratory Society	Full	General	General	There are concerns over the individual components within the algorithm, specifically: <u>Spirometry</u> There was widespread concern at the use of spirometry to establish a diagnosis of asthma, and the apparent imposition of the adult threshold of FVC/FEV1 ratio of 70%. We are aware that the developers of the Global Lung Function Initiative (GLI) 2012 spirometry reference equations and the large number of international organisations have already written to you regarding this issue. We would reiterate their conclusion that there is no evidence whatsoever that the proposed fixed ratio for FEV_1/FVC is clinically acceptable, and that they	Thank you for your comment. Spirometry: A diagnostic cut-off for obstructive airways disease in children needs to be given and the GDG considered that FVC/FEV1 ratio of 70% is reasonable in children aged 5-16 years. This threshold would make a slight difference to small number of children but is a compromise between usability and absolute scientific accuracy. GLI values were only in the white population. The GDG has added a footnote to the recommendations for the reference values in children for spirometry and BDR 'Or the lower limit of normal if the calculation is available in children'." Bronchodilator responsiveness: A diagnostic cut-off for bronchodilator reversibility in children needs to be given and the GDG considered that 12% is reasonable in children aged 5-16 years. The 12%

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				found no published studies which validate the use of the fixed ratio in asthma. As an example of how unrealistic the 70% cut off is, reference 22 states that the mean FEV1/FVC ratio among children with suspected and later confirmed asthma was 94% of predicted. <u>Bronchodilator responsiveness</u> There is no evidence for the 12% bronchodilator responsiveness cutoff in children – it is merely extrapolated from adult data. There was concern that the 70% cut off for obstructed spirometry is a high threshold and many members commented that they routinely test for bronchial reversibility if there is any suggestion of flow limitation on a flow volume loop and even if there was a restrictive pattern – many see examples of reversible restrictive lung volumes after bronchodilator inhalation and particular in the younger age group. Some respondents report have using a Bronchodilator Reversibility of 8-9% as being positive in children. "Diagnostic accuracy of the bronchodilator response in children" J Allergy	cut-off is a compromise between specificity and sensitivity. FeNO: We agree that FeNO values are age-dependent in children. A large study including >400 healthy children aged 4-17 years found FeNO to be between 15 and 25 ppb depending on age [Buchvald JACI 2005]. However the GDG felt cut-points were preferable to reference ranges for practical reasons and taking into consideration reference 185 [Verini M et al, 2010] the GDG considered that 22ppb as the lower cut-point is reasonable in children aged 5-16 years. The higher cut-point of 35 ppb is supported by Ciprandi G et al, 2013. In this study FeNO levels > 34ppb were predictive of bronchodilator reversibility. This cut-point is also supported by the ATS clinical practice guideline on the interpretation of FeNO. The paper cited does not provide evidence compelling enough to persuade the GDG to change the cut-off value. The study recruited a group of people with asthma and a non-symptomatic group (people without asthma who had never wheezed). Studies of this design were excluded as they do not represent the population in which the test will be

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				Clinical Immunol 2013;132:554-9 <u>Exhaled Nitric Oxide</u> Probably the greatest concern was the introduction of exhaled nitric oxide (FeNO) as part of the diagnostic algorithm. There was consensus that FeNO is not an asthma test and that there is clear evidence that FeNO in children is elevated in atopy independent of asthma. In clinical practice the differential diagnosis of high FeNO levels include asthma, atopy and constitutional elevation. In clinical practice normal/low levels makes clinicians rethink but not automatically exclude the diagnosis of asthma. The ENO threshold of >22ppb is based on a single study (reference 185, table 45, page 139). Yet the algorithm introduces an ENO cut off of 35 ppb, although there does not appear to be any evidence for this value. Reference 185 gives an accuracy of 56% for a cut off of >35ppb – good positive predictive value but poor negative predictive value. Knowing that ENO increases by 1ppb per year up to 12 years of age	used clinically (people with respiratory symptoms) and inclusion of healthy controls may lead to over estimations of specificity. Please note that the GDG made a high priority research recommendation in children to investigate the most clinically and cost effective diagnostic pathway. The GDG accepts this comment that currently there are no paediatric data for BDR. The GDG acknowledges that there is no clear cut-off for BDR that precisely separates asthma from non-asthma in children and that considerable heterogeneity in the BDR response exists. Demonstrating reversible airways disease is an important test to diagnose asthma and a cut-off has to be chosen. This is not different in children when compared to adults with asthma. Choosing a cut-off for bronchodilator reversibility is a compromise between sensitivity and specificity of the test. The reference cited Tse SM et al. Diagnostic accuracy of the bronchodilator response in children J Allergy Clin Immunol 2013;132:554-9 suggests good specificity of the 12% cut-off in children but

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				(http://www.thoracic.org/statements/resources/allergy-asthma/feno-document.pdf), it is not valid to use the same value for adults and children. <u>Peak flow variability</u> See comments above	poor sensitivity. Not surprisingly, when the threshold is lowered sensitivity increase with a concomitant decrease in specificity. In addition, many of the included studies were trying to distinguish between asthma and COPD so children may well be different. Distinguishing between asthma and COPD is not relevant for children. However, when scoping the guideline stakeholders requested more guidance in children and hence children of all ages have been included in the evidence reviews. Regarding FeNO, please see the clinical and cost effectiveness evidence in chapter 16 which includes explanation of the cut-off thresholds given for children (section 16.6). FeNO is recommended as a test in children with symptoms of possible asthma, not in children without respiratory symptoms. In this context the fact that it might be elevated because of atopy is a somewhat specious objection to its use. Moreover, it is not advocated as the only test to be used. The diagnostic cut-off value for FeNO in children is not the same as that for adults.

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British Paediatric Respiratory Society	Full	General	General	Trial of treatment We were disappointed that there was no clearer guidance on how to perform and assess and document a trial of therapy. Certainly this is widely used in children less than 5 years, and for many older children. Exercise testing There was disappointment that the benefits of exercise testing children to delineate different wheezing phenotypes was not recognised within the document.	Thank you for your comment. Trials of treatment are certainly used traditionally, but there is little formal evidence to support their use, and no comparisons of different methods of performing or evaluating them. Regarding exercise challenge testing, please see chapter 20. The diagnostic accuracy of exercise challenge tests did not support their use in the diagnostic pathway for children (small studies of low quality with poor reference standards which showed moderate sensitivity). The GDG acknowledged that the evidence for exercise testing was more favourable in children than adults, but still insufficient to make a national recommendation to support its use in the diagnosis of asthma. However, the GDG made a high priority research recommendation to investigate the utility of exercise challenge testing in children to diagnose asthma.
British Society for Allergy & Clinical Immunology	Full	4	4	The use of validated questionnaires for the monitoring of asthma control, particularly the ACT which has been validated in the field against the GINA asthma control categories is likely to be most efficacious, particularly in primary care, and should be part of routine asthma management practise. This is always provided that the	Thank you for your comment.

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				diagnosis of asthma has been made and that there is no co-morbidity contributing to symptoms: no "monitoring strategy" will pick up these features automatically.	
British Society for Allergy & Clinical Immunology	Full	8	Initial clinical assessment	Occupational asthma is also frequently associated with a lag period of 6 months or so after commencing a triggering occupation during which sensitisation occurs. Asthma is then preceded by symptoms of allergic rhinoconjunctivitis. This time course can sometimes be helpful in diagnosis: many people with or without asthma feel better on holiday.	Thank you for your comment.
British Society for Allergy & Clinical Immunology	Full	8	Objective tests	This section is misleading because the diagnosis of asthma is not based on obstructive spirometry alone but on variable airflow obstruction: spirometry need not be obstructive on first encounter but may emerge after monitoring. It is agreed that measuring FEV1/FVC ratio with a spirometer may be a more reliable substitute for PEF monitoring to achieve this goal, particularly in a primary care setting, since it captures additional data including a flow/volume loop and might better differentiate obstruction from a restrictive defect.	Thank you for your comment. Please see the diagnostic algorithms which show the subsequent tests that should be performed following non-obstructive spirometry,
British Society for Allergy & Clinical Immunolo	Full	8-9	Objective tests	It is very hard to see how "offering" FeNO in addition to lung function monitoring to diagnose asthma can possibly be cost effective in primary care. Baseline measurements are very variable between individuals, are affected by concomitant atopic upper airways inflammation and in many cases not easy to interpret,	Thank you for your comment. A robust health economic analysis was built to justify the use of FeNO as part of a diagnostic pathway. Pathways that included routine FeNO tests provided higher health outcomes at a lower cost than strategies which did not routinely offer FeNO tests. This result

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gy				particularly if the patient has been exposed to steroid of any sort. For these reasons, FeNO should not be recommended by NICE in primary care. Similarly it is hard to see how FeNO could add to the diagnostic accuracy of direct bronchial challenge in a cost effective way.	held even when the cost of FeNO was vastly changed, please refer to the sensitivity analyses in section M.3.2 in the appendix M. This analysis showed that if the cost of FeNO increased to £90 per patient, it remained cost-effective. The systematic clinical review found that FeNO had a high diagnostic accuracy. The studies identified in this review were completed on individuals who presented with asthma symptoms therefore any issues related to baseline differences would have been captured in these studies.
British Society for Allergy & Clinical Immunology	Full	9	Children younger than 5 years	When diagnosing respiratory symptoms as asthma subjectively in children under 5 years old, failure of the symptoms to respond to anti-asthma treatment is very much against a diagnosis of asthma, Thus, if the diagnosis is uncertain, all existing treatment should be stopped before objective testing.	Thank you for your comment. Please see recommendation 1.2.1 which states that a diagnosis of asthma cannot be made in children under 5 and that if asthma is still suspected when they are old enough to take part in objective tests they should be performed and the diagnosis reviewed. The GDG has added bullet points to recommendation 1.2.1 to reflect how existing treatment should be managed when the child is able to perform objective tests.
British Society for Allergy & Clinical Immunolo	Full	9	Monitoring asthma control	It is hard to see why ACT should simply be "considered" (this implies that the intervention will do more good than harm, and be cost effective, but that other options may be similarly cost effective): which other options are there to "consider"?	Thank you for your comment. In NICE convention, the words "offer" and "consider" refer to strength of the evidence. During their discussion of the evidence, the GDG agreed that there was a clinically important benefit of monitoring using asthma control questionnaires for some outcomes. However,

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gy					evidence was only available from two studies in adults with small sample sizes. The evidence quality was low or very low for most outcomes by GRADE criteria. This means the GDG was less confident that the effect estimate represented the true effect of monitoring. The GDG agreed that monitoring using asthma control questionnaires is likely to have clinical benefit, but chose the recommendation wording to reflect the strength of the evidence and its uncertainty.
British Society for Allergy & Clinical Immunology	Full	9	Monitoring asthma control	Monitoring and teaching of inhaler technique can be greatly facilitated by devices such as the 2Tone, the Ames meter and the Turbutest. Consideration should be given to making these available in every centre where "asthma checks" are performed. It is surprising that these devices are not mentioned anywhere in the document, although it would be challenging to demonstrate that they are "cost effective". Their usefulness to check adequate technique with dry powder inhaler devices is also being somewhat undermined by the plethora of new DPI devices appearing on the market. What is the evidence that inhaler technique should be checked annually as opposed to more often? According to the National Review of Asthma Deaths inhaler technique must be checked by the pharmacist every time a new inhaler is	Thank you for your comment. For this review, only RCT studies were included assessing the effectiveness of monitoring inhaler technique vs either no monitoring or different methods of monitoring on patient outcomes. Observational studies were not included in this review. Evidence was included on the effectiveness of the 2Tone Trainer device (see chapter 29). No evidence was identified for the Ames meter and the Turbutest. Due to the limited amount of RCT evidence on the best method of monitoring inhaler technique, the GDG made a high-priority future research recommendation to assess the best method for monitoring inhaler technique. Further details on the high-priority research recommendation made can be found in appendix N.

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				prescribed and this should be mentioned in this guidance.	
British Society for Allergy & Clinical Immunology	Full	10	Algorithm: Box 3:	Patients are often unaware of triggers (e.g. house dust mite exposure), or be in denial (pet exposure). Therefore allergy testing to aeroallergens, to identify triggers, at this point should be mandatory. Ref. Bobb et al. Effects of allergen and trigger factor avoidance advice in primary care on asthma control: a randomised-controlled trial. *Clinical and Experimental Allergy* 2010 **40**; 143-52	Thank you for your comment. The GDG agrees that allergy testing to aeroallergens to identify triggers is important and has added a recommendation to reflect this. However, the diagnostic accuracy of allergy tests to diagnose asthma was not supported in the review of the best available evidence.
British Society for Allergy & Clinical Immunology	Full	11	Algorithm B1	Skin prick testing is not of course diagnostic of asthma but should be mandatory for suspected allergic triggers, and does encourage enquiry about allergic triggers and also allows allergy to be excluded which is important in a number of asthma phenotypes. Exercise challenge (for example getting a child to run up the stairs and demonstrating bronchoconstriction) can be a very useful and cost effective means of diagnosing asthma: why has it been ostracised? Monitoring of FeNO once again appears from the algorithm to be superfluous since it does not preclude monitoring of FEV1/FVC (and why not PEF as well): conversely, is the diagnosis of asthma to be discarded if spirometry is normal and FeNO<25 ppb on a single occasion – this is not necessarily the	Thank you for your comment. The GDG agrees that skin prick tests are important to identify triggers and this is supported in the guideline (section 15.6); and the GDG has added a recommendation to reflect this. The diagnostic accuracy of skin prick tests to diagnose asthma was not supported in the review of the best available evidence; please see chapter 14. Regarding exercise challenge tests, please see chapter 20. The diagnostic accuracy of exercise challenge test did not support use in the diagnostic pathway for children, however, the GDG made a high priority research recommendation to investigate the utility of exercise challenge testing in children to

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				case?	diagnose asthma. Regarding the last point, there is a 3-step point to get to a negative test after 2-4 weeks of PEFv monitoring.
British Society for Allergy & Clinical Immunology	Full	13	Algorithm C	Same comments as for the adult algorithm (no. 8 above)	Thank you for your comment. Please see above response.
British Society for Allergy & Clinical Immunology	Full	14	1.1.1	Do people know what "wheeze" means? Nocturnal symptoms?	Thank you for your comment. "Wheeze" is defined in the glossary in the full guideline; please refer to page 306 (consultation version, or page 309 in the final version).
British Society for Allergy & Clinical Immunology	Full	P14	1.1.3	Is it worth stressing that it is often helpful to examine the upper respiratory tract as well?	Thank you for your comment. Guidance on how to do a physical exam is outside the remit of this guideline.

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British Society for Allergy & Clinical Immunology	Full	P14	1.1.4.	As point 8, Patients are often unaware of triggers (e.g. house dust mite exposure), or be in denial (pet exposure). Therefore allergy testing to aeroallergens, to identify triggers, at this point should be mandatory.	Thank you for your comment. The GDG agrees that allergy testing to aeroallergens to identify triggers is important and has added a recommendation to reflect this. However, the diagnostic accuracy of allergy tests to diagnose asthma was not supported in the review of the best available evidence.
British Society for Allergy & Clinical Immunology	Full	P15	1.1.7	Questions to reveal potential occupational asthma could be amplified as in comment no. 2 above.	Thank you for your comment. The wording of the recommendation on occupational asthma is based on evidence on the accuracy of identifying occupational asthma by asking if symptoms are better away from work.
British Society for Allergy & Clinical Immunology	Full	P15	1.1.9	Is quality control of calibration of spirometers and their correct usage taken as read?	Thank you for your comment. The short answer is "yes". Ensuring proper administration of tests is outside the remit of this guideline. We state clearly in the LETR that the diagnostic accuracy of the algorithm is dependent on the correct administration of the objective tests.
British Society for Allergy & Clinical	Full	P16	1.1.15	Allergy testing is not of course a diagnostic test for asthma but arguably should be an integral feature of the asthma "work up" in all patients, and particularly where allergen exposure is suspected to be a significant trigger	Thank you for your comment. The GDG agrees that allergy testing to aeroallergens to identify triggers is important and has added a recommendation to reflect this. The diagnostic accuracy of allergy tests

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Immunology				as well as a useful test to exclude allergy as a potential trigger. So skin prick tests and measurement of specific IgE to common aeroallergens should be used to identify potential triggers. Measurement of serum total IgE should not be used under any circumstances.	to diagnose asthma was not supported in the review of the best available evidence.
British Society for Allergy & Clinical Immunology	Full	P18	1.2.3 and 1.2.5	This section is over complicated and confusing. FeNO may be used in established asthma in a secondary/tertiary care setting as a surrogate for sputum eosinophilia when induced sputum is not avilable and can be used under certain circumstances to predict and monitor exacerbations and response to treatment, but only in those patients who are known to have elevated FeNO during poor asthma control. These circumstances would benefit from clear definition.	Thank you for your comment. FeNO has been shown to be cost effective by both the original health economic model developed as part of this guideline's cost effectiveness analysis and by the NICE DAP health economic model. The GDG disagrees that the implementation of the diagnostic algorithm is prohibitively complex. Patients who present to their GP with mild symptoms of asthma can perform spirometry, BDR and FeNO tests during a follow-up appointment with the practice nurse to get a positive diagnosis of asthma. A small proportion of patients with diagnostic uncertainty will go through the longer route in the diagnostic pathway in order to obtain further objective testing evidence of asthma. The GDG considered that patients with intermittent symptoms should be called back for further review.
British Society	Full	P21	1.3.2	Consider taking an ACT score mandatory when assessing asthma control (see comment no. 1 above)	Thank you for your comment. Please see chapter 23, in particular section 23.6. The strength of the

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for Allergy & Clinical Immunology					recommendation is based on a review of the best available evidence. The GDG did not consider that the evidence was strong enough to support an 'offer' recommendation for ACT.
British Society for Allergy & Clinical Immunology	Full	P21	1.3.5	Measurement of FeNO may suggest detect poor compliance with inhaled steroid therapy in asthmatic patients who remain symptomatic, since steroids strongly suppress iNOS expression. Nevertheless, it would be surprising if this increased the "pick up" rate of poor compliance over good clinical intuition, especially cost effectively. Compliance is most often poor because it is not encouraged in th first place. Finally, even if poor compliance is demonstrated or strongly suspected, it cannot be enforced but only encouraged, which should be a routine feature of asthma management anyway	Thank you for your comment. Recommendation 1.3.5 is taken from the NICE DAP on FeNO.
British Thoracic Society	Full	General		The BTS notes the extensive work that has gone into the document and recognises the need for objective diagnosis of asthma and the significance of inflammometry. There is extensive literature review and review of evidence for existing tests and this is to be applauded in highlighting where further research is required to evaluate current diagnostic tests. We fully appreciate the methodology and that recommendations are restricted by the constraints of a paucity of reliable evidence for some diagnostic tests in common use. The	Thank you for your comment.

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				specialist advisory group for asthma has received a number of comments from members of the British Thoracic Society which will be presented here.	
British Thoracic Society	Full	General		The diagnostic pathway is felt to be overcomplicated for those expected to implement it with the inclusion of multiple diagnostic tests that will require a significant investment and capital cost in obtaining equipment (e.g. Exhaled Nitric Oxide Analyser) or obtaining access to lung function equipment / trained personnel e.g. challenge testing.	Thank you for your comment. The primary aim of this clinical guideline was to produce the most clinically and cost effective way to diagnose asthma accurately. The GDG acknowledge that the implementation of some objective tests in primary care will require initial investment and training. However, the health gains and improvements in patient outcomes have been shown to be clinically effective as well as cost effective for the NHS; please see the health economic analysis in appendix M. The NICE Implementation team will produce support materials to facilitate uptake of the guideline into clinical practice. The GDG disagrees that the implementation of the diagnostic algorithm is prohibitively complex. Patients who present to their GP with mild symptoms of asthma can perform spirometry, BDR and FeNO tests during a follow-up appointment with the practice nurse to get a positive diagnosis of asthma. Of these tests, only FeNO is new. A small proportion of patients with diagnostic uncertainty will

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					go through the longer route in the diagnostic pathway in order to obtain further objective testing evidence of asthma. The GDG considered that patients with intermittent symptoms should be called back for further review.
British Thoracic Society	Full	General		It is felt by many that the diagnostic pathway should be aligned with BTS / SIGN guidelines and that this may cause confusion among the healthcare community. The organisations should consult and work together to reduce conflict.	Thank you for your comment. The GDG does not feel that the recommendations on diagnosis in the NICE guideline are vastly different from that of BTS/SIGN. The NICE guideline provides more detail of when to perform certain objective tests. The major difference is around FeNO testing. The FeNO sections in the diagnosis chapter of the BTS/SIGN guideline are not as up to date as those in the NICE guideline, and the GDG feel that the inclusion of FeNO in the diagnostic pathway is amply justified.
British Thoracic Society	Full	General		Cost calculations do not appear to include capital investment indiagnostic equipment and training, which would be substantial. Neither is the costing for review particularly accurate in terms of GP / nurse time in primary care.	Thank you for your comment. All cost calculations include capital investments, see appendix M. The costs take into account the initial cost of the equipment needed and how many times the equipment could be used until it was replaced. GP and nurse times were based on expert consensus and when they were doubled this did not impact the model results.
British	Full	149	Relates	The economic modelling dictates the order of	Thank you for your comment. In the pathway, apart

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Thoracic Society		and 140	to economic modelling	investigations in the diagnostic pathway however this appears to be flawed. It is felt that the unit cost for measuring eosinophil blood count (a test that may already be historically available for many patients) would be £82.33 mainly accounted for by the inclusion of GP time: 1 for referral and one to discuss the results. This does not appear to feature on other tests e.g. Cost of FeNo does not include this GP appointment and therefore is not comparable. It would be expected that any test would require the same referral and explanation of test results and by the same reckoning would add £72 to the test bringing it to a total of £82.34 - £85.66.	from PEF, all the test results are conducted and available on the day the individual performs the test. However with eosinophil blood count tests as the results would need to be sent off to a lab to be interpreted there would need to be a minimum of two visits to complete this test. This cost represents the cost of eosinophils as a standalone test rather than the cost as part of a diagnostic pathway. This has now been made clearer in the guideline. It is worth noting that eosinophils were not evaluated in the economic model as the GDG felt there was no point in the pathway where the results from an eosinophil test would overturn a diagnostic decision based on all the previously done tests. This was due to the low diagnostic accuracy identified in the clinical review.
British Thoracic Society	Full	General		The remit of the guideline is to ensure correct diagnosis of asthma and evaluate those tests that are required to effectively make that diagnosis objectively. However as acknowledged in the introduction there is currently no gold standard test available and this makes it difficult to evaluate each test against another. Also it is also recognised that asthma is a term for a number of conditions that may include a spectrum of inflammatory airway disease, airflow obstruction and bronchial hyper-responsiveness. ,We would recommend that the existence of forms of asthma that do not include	Thank you for your comment. The GDG acknowledges that the absence of a gold standard test for asthma makes diagnosis difficult. The exact biology underpinning asthma endotypes continues to evolve at a rapid pace and is beyond the introduction to this guideline. The exact prevalence of T2 low inflammation has yet to be determined and indeed many individuals with supposed T2 low inflammation may simply become T2 high on withdrawal of inhaled corticosteroids. It is likely that any future iteration of this guideline will include

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				eosinophilic Th2 inflammation for example be acknowledged in the introduction as this may allow clinical judgment to be used when using guidelines.	guidance on what are currently perceived to be novel biomarkers.
British Thoracic Society	Full	General		Evaluation of tests require a standard of a clinical diagnosis of asthma and one other objective test. This implies that the comparison objective test used is essentially a "gold standard". Therefore sensitivity / specificity for each test is difficult to compare as for example FeNO was compared to reversibility and BCT in one study however more weight is placed on FeNO testing in the diagnostic pathway.	Thank you for your comment. You are correct, but in the absence of a gold standard test a degree of pragmatism is necessary. The GDG defined the reference standard as physician diagnosis plus an objective test. The GDG specified the criteria for objective tests used as the reference standard in order to maximise the accuracy of the reference standard. Only where evidence was not available using these objective test, was evidence considered using a difference reference standard and the evidence quality was downgraded. The GDG agreed that this was the most pragmatic approach given the multiplicity of reference standards used in the literature.
British Thoracic Society	Full	General		It is not immediately obvious why an alternative strategy was not considered; namely that of using (repeated) clinical history and examination supported by peak flow monitoring and response to trials of therapy, with the reservation of spirometry, FeNO testing and if necessary bronchial challenge testing in cases of doubt or difficulty in diagnosis. (After all asthma is a variable condition which can vary over time). Should we allow for clinical judgment?	Thank you for your comment. The strategy you describe is commonly used, but there is little rigorous analysis of its efficacy. We note that BTS/SIGN also found no good trial evidence and that the use of a trial of treatment is graded as a Good Practice Point for children and a Grade C recommendation for adults within that Guideline. It is also a time consuming process, and the only objective element of it, PEF variability, is known to

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					have low sensitivity as a test for asthma. The proposed diagnostic sequence allows its use in cases of genuine doubt (see algorithms B1 & C) but encourages the use of more objective tests beforehand. All NICE clinical guidelines allow for, and do not replace, clinical judgement.
British Thoracic Society	Full	General		There should be an evaluation of a trial of treatment (failure to respond as well as response) and we would be grateful for a response as to why this has not been included.	Thank you for your comment. The GDG disagrees that trial of treatment should be given on the basis of symptoms alone. Trials of treatment are certainly used traditionally, but there is little formal evidence to support their use. We note that BTS/SIGN also found no good trial evidence and that the use of a trial of treatment is graded as a Good Practice Point for children and a Grade C recommendation for adults within that Guideline. A counter view is that they can lead to misdiagnosis when a natural improvement in symptoms coincides with, and is spuriously attributed to, introduction of asthma therapy. The proposed diagnostic sequence allows their use in cases of genuine doubt (see algorithms B1 & C) but encourages the use of more objective tests beforehand. The diagnostic endpoints do factor in reviewing the

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					diagnosis of asthma based on response to treatment.
British Thoracic Society	Full	General		Bronchial challenge testing with methacholine (only available in secondary care and not always there) is accorded a significant role in cases of doubt in the conclusions from spirometry and FeNO testing. Peak Flow Monitoring – an inexpensive, easily available and widely used method of documenting objective evidence of variable airflow obstruction – is retained but only for further clarification in cases of doubt or difficulty having used the more expensive and less easily available diagnostic aids first. This did not particularly fit with improvements in specificity	Thank you for your comment. Currently bronchial challenge testing is available in secondary care but the GDG acknowledge that this service provision is not widespread. Hospitals with a lung function laboratory should be able to perform challenge tests. The GDG acknowledge that patients in some areas of the country may need to travel to undertake a bronchial challenge test. The current coverage is unknown however if there is more demand in future this service provision will become more widely available. In all the pathways PEF tests are always conducted before bronchial challenge tests. Challenge testing is retained for individuals that have diagnostic uncertainty after: spirometry, bronchodilator reversibility tests, FeNO and PEF.
British Thoracic Society	Full	General		The principle health economic argument in favour of rendering the diagnostic process substantially more complex and expensive, and substantially more dependent on referrals to secondary care services , rests on the assumption – supported by reference to a single Canadian study in adults conducted in 2005-7 – that there is substantial overdiagnosis and unnecessary	Thank you for your comment. In the arm that made this assumptions two more assumptions also imposed were that asthma is always perfectly diagnosed (sensitivity = 100%) and the costs of doing so are zero. Even with these assumptions in place the strategy was not cost-effective. The reference cited is the best evidence we have for

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				treatment of asthma. It is therefore inferred that savings in reduced treatment costs would offset the cost of a more complex diagnostic process. The cited study was based on a telephone survey for recruitment, and its authors acknowledged that volunteer bias may have led to an overestimate of the misdiagnosis rate.	what level of diagnosis may be and this is supported by numerous other references. A sensitivity analysis was also conducted whereby the specificity of 'current practice' was increased by 10% and the recommended diagnostic algorithm remained cost-effective at a £20,000 per QALY threshold.
British Thoracic Society	Full	General		The use of spirometry (20-30m) and ACT (10m) plus variability will have large implications for funding of additional resource required to deliver this in primary care - this does not appear to be addressed in the documentation.	Thank you for your comment. The GDG disagrees that it takes 20-30 minutes to perform a spirometry test and 10 minutes to do an ACT, especially seeing as it is likely they would have performed these tests before. As the individual will be having a review to monitor their asthma anyway it is likely that doing spirometry and ACT will replace some time spent of the review as opposed to adding additional time. The GDG noted the reduction in unscheduled healthcare utilisation would also free up additional resources. We agree that measuring reversibility takes 20-30 minutes, but this is only applicable to those (a minority) who have airflow obstruction at the time of testing and therefore does not represent additional resource.
British Thoracic	Full	General		Direct bronchial challenge test with histamine and methacholine: These tests are complex to perform, not	Thank you for your comment. The clinical evidence for direct bronchial challenge tests found that they

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Society				available in primary care, not consistently available in secondary care clinics and only likely to be performed once. After a complex analysis of their cost effectiveness in various places in a diagnostic algorithm their use is recommended by the GDG in persons over age 16 as part of a strategy to clarify the diagnosis in situations of inconsistent results from other diagnostic tests. It is acknowledged that these tests are expensive to perform and interpret but also recognises that a negative test does not exclude asthma, nor rule it out.	had high sensitivity and specificity relative to all other diagnostic tests for asthma and have therefore been included in the diagnostic process. They will not be required for most of those with suspected asthma. We agree that bronchial challenge tests will be undertaken within secondary care.
British Thoracic Society	Full	General		The main paper referenced to justify the work requires further evaluation and requires critique: Aaron et al is quoted as a source to explain that there may be a possible misdiagnosis of asthma in 30% of patients already diagnosed. This is a retrospective study seeking to confirm whether patients on treatment have objective markers of asthma i.e evidence of bronchial hyperesponsiveness. This did not take into account FeNO or other measures of airway inflammation that features prominently in this guideline. In the diagnostic pathway proposed a diagnosis of asthma may have been considered in some of the cases where asthma was excluded. It is not clear either whether those patients that no longer had objective evidence of asthma had positive tests at the point of their original diagnosis (asthma is a	Thank you for your comment. The GDG acknowledges that the Aaron paper was cited too frequently at the expense of other relevant evidence. This has now been updated. For the statement "almost a third (30%) of adults do not have clear evidence of asthma" the guideline development group is aware of consistent evidence and cross-sectional surveys (5 references are given below) that suggest a large proportion of people treated for asthma at a single point in time do not have objective supportive evidence, or had normal objective tests. This is not to say that they were all misdiagnosed. The other possibilities are that their treatment has been so effective as to make all objective findings normal (in which case stepped-

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				variable disease). There is a significant risk of selection bias in the population studied 540 (44 dropped out) patients were studied relying on patient response to telephone screening.	down treatment should be considered), or that spontaneous changes in an intrinsically variable condition have meant that, at that moment in time, all objective findings were normal. Without incidence studies with tests done at the time of presentation and diagnosis, the true figure is unknown. The GDG accepts that over-diagnosis has been emphasised in the write-up more than under-diagnosis, and that both are important. Both were considered equally when reviewing the evidence, and the guideline has been amended to reflect this. 1. Starren ES, Roberts NJ, Tahir M, O'Byrne L, Haffenden R, Patel IS, Partridge MR. A centralised respiratory diagnostic service for primary care: a 4-year audit<http://www.ncbi.nlm.nih.gov/pubmed/22430040>. Prim Care Respir J 2012; 21(2): 180-186 2. Linden Smith J, Morrison D, Deveau C, Hernandez P. Overdiagnosis of asthma in the community<http://www.ncbi.nlm.nih.gov/pubmed/15045041>. Can Respir J 2004;11(2):111-16. 3. Aaron SD, Vandemheen KL, Boulet LP, et al.

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					Overdiagnosis of asthma in obese and nonobese adults<http://www.ncbi.nlm.nih.gov/pubmed/19015563>. CMAJ 2008;179(11):1121-31. 4. Marklund B, Tunsater A, Bengtsson C. How often is the diagnosis bronchial asthma correct<http://fampra.oxfordjournals.org/content/16/2/112>? Fam Pract 1999;16(2):112-16. 5. Shaw D, Green R, Berry M, Mellor S, Hargadon B, Shelley M, McKenna S, Thomas M, Pavord I. A cross-sectional study of patterns of airway dysfunction, symptoms and morbidity in primary care asthma http://www.ncbi.nlm.nih.gov/pubmed/22786814 Prim Care Respir J. 2012 Sep;21(3):283-7. doi: 10.4104/pcrj.2012.00057
British Thoracic Society	Full	153		It is stated that "A FeNO test could easily be performed after a spirometry or a BDR test at a low marginal cost". Silkoff et al. *Am J Respir Crit Care Med.* 1999; 159:940-4 Showed that: "As early as 1 min after spirometry, ENO fell by 13% and 10% in the normal and asthmatic subjects, respectively. In both groups, ENO returned to baseline over 1 h." Therefore a further visit would be required for diagnosis incurring further costs and therefore would require reassessment of the algorithm.	Thank you for your comment. Silkoff's is a small study using old FeNO equipment. More recent, larger studies do not necessarily reproduce those results (eg. Garriga T et al. Respiration 2012. 83:239-244). Both FeNO and BDR tests could be performed in a single visit.
British Thoracic	Full	General		It appears to take a min of 3 tests to make a diagnosis, with a max of 5 to finally secure a formal diagnosis. This	Thank you for your comment. The primary aim of this clinical guideline was to produce the most

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Society				appears to be very complicated and time consuming for a large amount of patients presenting with respiratory symptoms consistent with possible asthma.	clinically and cost effective way to accurately diagnose asthma based on the best available evidence. The GDG disagree that the implementation of the diagnostic algorithm is prohibitively complex. Patients who present to their GP with mild symptoms of asthma can perform spirometry, BDR and FeNO tests during a follow-up appointment with the practice nurse to get a positive diagnosis of asthma. A small proportion of patients with diagnostic uncertainty will go through the longer route in the diagnostic pathway in order to obtain further objective testing evidence of asthma. The GDG considered that patients with intermittent symptoms should be called back for further review.
British Thoracic Society	Full	General		The guidelines do not specify what to do if there are symptoms but results are negative. This could be a third of patients. Do they get referred too? This needs confirmation as it is often this group that requires specialist input. Also the diagnostic pathway finishes on some limbs at "consider alternative diagnosis". Further guidance may be required regarding this.	Thank you for your comment. It is outside the remit of this guideline to give national recommendations on what those other diagnoses might be, however, the main differentiate diagnoses were modelled in the original health economic model analysis; please see appendix M,
British Thoracic Society	Full	General		The role of primary care and secondary care involvement is not clearly defined and this should be commented upon. Where should these tests take place?	Thank you for your comment. It is not possible to make recommendations on where objective tests should be performed as it will vary. Service delivery aspects of the recommendations are outside the remit of this guideline.

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British Thoracic Society	Appendices	22-23		We would wish to explore the impact of declared conflict of interest regarding Aerocrine and Prof Mike Thomas and his withdrawal from discussions surrounding FeNO.	Professor Thomas did not participate in the discussions on FeNO in accordance with NICE's policy on Conflicts of Interest (see appendix B).
British Thoracic Society	Full	General		Carrying out spirometry in children is often difficult. First attempts at spirometry are often unreliable and yet this guideline puts a big emphasis on this initial test. BDR testing is only of any value if the spirometry is reliable and reproducible and it is common in children to get false positives. Peak flow is an easier test to perform and yet low peak flow for age and change in peak flow with bronchodilator have not been assessed at all (only peak flow variability over 2 weeks) Overall this guideline over simplifies the execution and interpretation of these tests, particularly in children.	Thank you for your comment. The GDG acknowledges that spirometry is difficult in children. However, as the BTS/SIGN guideline states, it is possible to do these tests in children over 5 years of age and we believe that increasing familiarity and practice will improve the proportion of accurate tests. Regarding peak flow reversibility, bronchodilator response measured using PEF and FEV1 was searched for but no evidence was found for PEF reversibility – please see the protocol in table 26 on page 95 of the full guideline (consultation version, or page 97 of the final version) and the 'linking evidence to recommendations' section on page 102 (consultation version, or page 104 of the final version) which says "No studies were identified using PEF to measure the extent of bronchodilator reversibility."
British Thoracic Society	Full	General		Very few children under 7 or 8 will be able to perform a FENO measurement and most children and adults will need several attempts to master the technique. There are very few data on FENO as a diagnostic tool in children. Only one paediatric specific study is included	Thank you for your comment. The GDG disagrees that a FeNO test in adults is difficult and considers that FeNO is an extremely simple test to perform and can be done in primary care. Although many adults take more than one attempt to get a reading,

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				and had a sensitivity of only 57%.	since each attempt takes less than a minute it is unusual not to be able to get a reasonable reading within 5 minutes. Regarding children, the GDG acknowledges that some very young children may require a few attempts but should be able to perform the manoeuvre and achieve the flow rate needed. The FeNO machine is designed for older people – children do find it difficult. Some children will and some children won't be able to, but it is worth trying. The GDG has added a footnote that 'at the lower end of the age range there will be varying abilities and if the child cannot perform FeNO the principles in recommendation 1.2.1 should be followed until the child is old enough to perform the FeNO test adequately'. The GDG felt that spirometry should be done in children aged 5 onwards.
British Thoracic Society	Full	General		There is an important interaction between atopy and FENO with some studies in children suggestion that FENO is more reflective of atopy than asthma per se (Thorax 2010 Mar;65(3):258-62)which is an important consideration in paediatric practice given that most	Thank you for your comment. You are correct, but the recommendations cover use of FENO in people with symptoms suggestive of asthma, not as a screening test in the general population or in people with symptoms suggestive of other atopic disorders.

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				children with asthma are atopic (at least 85%)	
British Thoracic Society	Full	General		The introduction states that the guidelines cover young children aged 0-5 years, however, almost all the data presented are for children aged 1-5 years (infants are usually excluded from studies in view of the overlap with bronchiolitis)	Thank you for your comment. Specific recommendations have been made for children aged 0-5 years based on GDG consensus where there was no available evidence. When scoping the guideline stakeholders requested more guidance in very young children and hence children of all ages have been included in the evidence reviews, despite the unlikeliness of any evidence in the very young age group.
British Thoracic Society	Full	General		cACT: It is also stated that there is no MID for the cACT. Vorrend's study in JACI suggests a 2 point difference in cACT is significant (1.6 (95% CI: 1.1 – 2.01) JACI 2014;133(6);1599-605	Thank you for your comment. The MIDs used to determine clinical importance of the effect of an intervention were chosen from the literature by the GDG at the protocol development stage. The Vorrend paper mentioned was published after the cut-off point for the literature searches for the guideline and therefore cannot be included in the evidence. However, we have reviewed the evidence in the guideline for any instances in which a different MID to that set by the GDG would change the decision of clinical importance. Using the MIDs stated in the Vorrend paper (1.9 for ACT and 1.6 for cACT), there was no difference in the clinical importance for this outcome in any of the evidence reviews.
Cochrane	NICE	18	1.1.21	Is there a place for exercise challenge in those people	Thank you for your comment. The diagnostic

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Airways Group				who have a clear history of exercise-induced wheeze and normal spirometry at rest?	accuracy of exercise challenge test did not support use in the diagnostic pathway for children, however, the GDG made a high priority research recommendation to investigate the utility of exercise challenge testing in children to diagnose asthma. In adults the GDG made a 'Do not' recommendation for exercise challenge testing because the diagnostic accuracy of this was shown to be poorer than that of the diagnostic pathway.
Cochrane Airways Group	NICE	21	1.3.5	The current recommendation is unhelpful. If you are going to suggest FENO for monitoring in those who are symptomatic despite ICS, surely you have to give some information about how to do this, and not just cite DG12? It is not straight forward to know how FENO levels should be used in practice (see next comment on Full draft).	Thank you for your comment. The cross-reference to the NICE DAP was a requirement for consistency. The recommendation in favour of using FeNO for monitoring in certain circumstances is taken from the DAP.
Cochrane Airways Group	Full	233	2nd para	The GDG point out that "diverse algorithms" were used in the clinical trials of FENO, but do not mention the safety nets of capping ICS dose or carrying out other investigation (such as sputum eosinophil measurements) in those who end up on high doses of ICS in the trials. The suggested advantage of checking compliance in the first paragraph is theoretical (rather than derived from the trials, since there are no FENO trials in section 28 on adherence, p 249) and any	Thank you. The recommendation for FeNO monitoring is couched in terms of it being an option. It should not lead to any person with asthma being over-treated purely on the basis of a spuriously high FeNO level.

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				theoretical benefit has to be balanced against the demonstrated danger of overtreatment with higher doses of ICS in those who actually are compliant but have a false-positive raised FENO level.	
Cochrane Airways Group	NICE	21	1.3	When do you stop monitoring asthma in people who no longer require treatment? How much do you need to monitor those who use a bronchodilator before exercise only (for example)?	Thank you for your comment. The point at which asthma has become quiescent is not part of the remit of this guideline.
Cochrane Airways Group	Full	General	General	**The GDG need to be aware that a small mean difference (with a 95% CI that is below the clinical minimally important threshold) is perfectly compatible with a significant increase in the proportion of people with have a benefit on treatments. It is not justifiable to rule out any clinically important benefit on the basis of the mean difference alone, without consideration of the results of a responder analysis in relation to the outcome concerned.**	Thank you for your comment. The GDG also considered other factors alongside the mean difference to base the decision of clinical important, such as the baseline values, the control group value at the end of treatment, and the GRADE rating. Responder analysis was not considered in the monitoring reviews due to the following limitations: responder analysis does not take into account the variation in response; where the outcome is measured on a continuous scale, the cut-off value used to determine a responder is an arbitrary point that needs to be determined and may differ between studies.
Department of Health	Full	General		Thank you for the opportunity to comment on the draft for the above clinical guideline. **I wish to confirm that the Department of Health has no substantive comments to make, regarding this**	Thank you for your comment.

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				consultation	
Department of Health, Social Services and Public Safety - Northern Ireland		General	General	A common reason for overdiagnosis is a child with a sole symptom of problem coughing, most likely recurrent viral bronchitis with 'cough receptor hypersensitivity' and with some developing persistent bacterial bronchitis. These conditions clearly overlap with asthma i.e. some have underlying often mild asthma. This area causes problems - because in Pre-school children 'tests' can't be done so diagnosis depends on a 'trial of treatment' therefore: **In general practice** the trial of treatment as diagnostic tests needs really tightened up - **this should be addressed in the NICE document but is not. NICE should be giving advice on how to undertake and document a formal 'trial of treatment'** e.g. diary cards so that if NO clear cut response is identified then treatment is stopped as 'trial' was negative.	Thank you for your comment. The GDG disagrees that trial of treatment should be given on the basis of symptoms alone, and particularly when the relevant symptom is as non-specific as 'cough'. Trials of treatment are certainly used traditionally, but there is little formal evidence to support their use. We note that BTS/SIGN also found no good trial evidence and that the use of a trial of treatment is graded as a Good Practice Point for children and a Grade C recommendation for adults within that Guideline. They can lead to misdiagnosis when a natural improvement in symptoms coincides with, and is spuriously attributed to, introduction of asthma therapy. The proposed diagnostic sequence allows their use in cases of genuine doubt (see algorithms B1 & C) but encourages the use of more objective tests beforehand. The GDG's view was that asthma cannot be diagnosed in children under 5 and that symptoms should be treated empirically and if asthma is still suspected when the child is old enough to perform objective tests the diagnosis should be reviewed on the basis of objective tests.
DGH	Full	Gener		The measure of reversibility user 12% and 200mls is	Thank you for your comment. Neither the BTS/SIGN

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		al		close to the statistically significant difference between measures of fev1, this is not the same as a clinically significant reversibility. There is ambiguity as the copd guidelines 2010 use 400mls for asthma. What do people with between 200-400mls have, it depends on which guidelines you look at The increased use of objective measures is a thing that should be encouraged, but the use of this diagnostic algorithm is going to far, this extent of FENO and challenge tests are not available and using resources for this will decrease services elsewhere	nor NICE COPD guideline makes a firm recommendation on the basis of a positive test. The more reversible the more evidence there is of asthma. The evidence reviewed in this guideline supports the thresholds specified in the recommendation; please see chapter 12. BDR does not have 100% sensitivity and specificity.
Digital Assessment Service, NHS Choices	Full	General	General	We welcome the guidance and have no comments on the content as part of the consultation	Thank you for your comment.
Durham Dales, Easington and Sedgefield	Full	General		Current guidance (SIGN) does not base diagnosis on any single criterion and includes a statement that 'a history of improvement of symptoms and lung function in response to therapy' increases the chance of asthma. Bush et al (BMJ 2015) quantify this as 12% reversibility for salbutamol, and also suggest that response may be	Thank you for your comment. We agree that diagnosis should not be based on any single criterion, hence our suggested pathway which relies on symptoms and more than one objective test. It is hard to respond to your request for a more

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				assessed over a longer period of time using inhaled steroids. NICE and QoF in England, require greater thresholds of 20% for their respective measurements, a figure which reduces but may not eliminate false positive diagnoses. Spirometry is very specific (p92) but poorly sensitive; only metacholine challenge appears to be sufficiently sensitive, but its routine use would be burdensome for both primary and secondary care, and we agree with its proposed reserve position in the algorithm. FeNO has, therefore, we imagine been chosen as companion to spirometry to provide diagnostic sensitivity? However, it performs less than ideally, and we, therefore, believe that a more pragmatic approach is required.	pragmatic approach without knowing exactly what you propose.
Durham Dales, Easington and Sedgefield	Full	General		The guideline should comment on standardisation of peak flow meters – 'EU meters' read > 10% more than standard meters.	Thank you for your comment. This guidance is outside the remit of this clinical guideline.
Durham Dales, Easington and Sedgefield	Full	86-92		Spirometry is technically more difficult than peak flow. As the test is ideally first undertaken when patients present with acute symptoms (to capture reduced FEV1 and FEV1/FVC <70%), we believe that diagnosis will be made more difficult. We are concerned that clinicians may avoid a diagnosis of asthma - there is evidence of this occurring when a diagnosis of depression was	Thank you for your comment. The GDG acknowledges that there is a paucity of diagnostic test accuracy data in children and hence made a high priority research recommendation to elucidate the best diagnostic pathway. The GDG has amended the recommendations for FeNO and BDR from 'offer' to 'consider' in children to reflect the

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				made overly complicated by the requirement to administer a PHQ-9 questionnaire. We wonder about the ability of children, in particular to perform the test (though some adults struggle), but would be reassured if NICE could provide evidence of the accuracy of testing in normal clinical practice in this young group.	evidence base. We agree that spirometry is technically more difficult than PEF, but when it can be performed it gives more useful information (and despite the difficulties, most adults and many children can produce satisfactory readings).. The GDG did not wish to recommend an inferior test for respiratory patients.
Durham Dales, Easington and Sedgefield	NICE	10		The finding of FEV1/FVC>70% appears crucial to further investigation. You state 'do not diagnose asthma based on any single test alone' Surely, the reverse is also true? What of the patient with a low normal FEV1/FVC, or the person in a stable phase (as patterns of asthma are very varied), who can demonstrate reversibility? The use of standard peak flow measurements over time should also be	Thank you for your comment. We assume you mean "do not rule out asthma on the basis of any single test". We agree, but this should not happen if our recommended diagnostic process is followed. You raise the possibility of misleading borderline results, but this is an issue in any diagnostic pathway in any disease; sensible clinical judgement is required when using any guideline.
Durham Dales, Easington and Sedgefield	Full	139		FeNO has a sensitivity of only around 70%, a value, which has in other (clinically unrelated) NICE guidance been determined to be insufficiently accurate to 'rule out' a diagnosis. In addition it is reported that FeNO values are inconsistent over time and the threshold values for the test appear to be subject to debate. We believe that FeNO may have a place in diagnosis but is insufficiently reliable to be a cornerstone.	Thank you for your comment with which we agree. FeNO has a place in diagnosis of asthma, but not as a sole test. The best available evidence supports the clinical and cost effectiveness of FeNO within the diagnostic pathway and therefore the GDG considered the initial investment worthwhile for long-term patient health gains. FeNO is an extremely simple test to perform and can be done in primary care.
Durham	Full	140	1	The cost-effectiveness calculation for FeNO does not	Thank you for your comment. The cost of FeNO

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Dales, Easington and Sedgefield				include the cost of a meter- we assume that firms provide free machines to promote their testing strips? It is, therefore, very important to recommend kitemarking or to provide data on reliability and between brand consistency.	does include the cost of a meter. This cost was taken from: Harnan S, Tappenden P, Essat M, Gomersall T, Minton J, Wong R et al. Measurement of exhaled nitric oxide concentration in asthma - NIOX MINO and NObreath, 2013. Available from: http://guidance.nice.org.uk/DT/13 *(Guideline Ref ID DG13)* This analysis cost the meter and calculated how many uses it would get before replacement to calculate the cost per patient. This cost was also extensively tested in a sensitivity analysis detailed in the economic write-up in appendix M.
Durham Dales, Easington and Sedgefield	NICE/Full	14/70	1.1.6/1-	We agree with the statement that an isolated clinical history of exercise should not be taken as a diagnosis of asthma, but we could not identify comments on the utility of post-exercise testing /variability in the assessment of asthma/exercise-induced symptoms. This is of particular significance to the quality of life of both children and adults, and its omission may give the	Thank you for your comment. Please see chapter 20 for the clinical and cost effectiveness evidence review of exercise challenge testing, which showed low sensitivity and specificity for diagnosing asthma. Symptoms after exercise are captured in the validated questionnaires on asthma monitoring. Please see recommendation 1.1.1 which states that

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				impression that an exercise history and assessment are no longer felt to be valuable.	a structured clinical history should be taken in people with suspected asthma.
Durham Dales, Easington and Sedgefield (DDES) CCG	Full	General		We welcome NICE's stated aim of improving diagnosis of asthma, but feel that with widespread concern about avoidable asthma deaths under-diagnosis has not been given sufficient recognition	Thank you for your comment. This change has been made.
Education for Health	Full	General		Whilst we would agree in with a more rigorous diagnostic process the presumption that asthma is over diagnoses in the UK (based on evidence from Canadian study) questions the validity of the guidelines. Also to be remembered that diagnostic testing is to support a detailed clinical history which as quoted time and time again as providing up to 80% of the diagnosis. New guidelines contradict the old ones looking at a diagnosis based on 'probability' If 30% of people are incorrectly diagnosed were the old guidelines actually being used.	Thank you for your comment. We are not aware of data which directly answer your question, but we agree with your suggestion that the existing BTS/SIGN diagnostic recommendations may not have been used sufficiently.
Education for Health	Full	1.1.9 1.2.1 1.2.2		This is going to be so difficult as practice nurses are not trained to an appropriate level and the quality of spirometry in general practice both the test and the interpretation is poor. With the diagnosis of asthma being variable a one off spirometry may give a false negative conclusion, often a series of readings are required to capture the variability	Thank you for your comment. We agree that there is work to be done on the quality of spirometry, but it is a better index of airflow obstruction than PEF and the GDG did not feel that it should shirk from recommending it. We do not entirely agree with you about the

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				and it is only through taking a detailed history and having that suspicion of asthma 'probability' that a well informed and educated clinician with an interest in asthma would continue. Likewise, improvement in FEV1 of 12% or more, together with an increase in volume of 200 ml or more, as a positive is already a topic of debate. Also depends on base line spirometry may not be much reversibility needed to bring to normal value, In contrast on occasions there is only a minimal improvement in FEV1 with SABA and only through trials of treatment due to a 'probability' of asthma continued with trials of treatment of ICS or oral therapy then found a significant improvement with repeat spirometry, comes back to history taking. It's challenging enough to get a young child to do peak flow reading let alone a quality assured spirometry trace. Actually the challenge is getting them to the clinic in the first place hence the need for better education and training to support child care workers / teachers. Whilst we agree either spirometry or "measurement of peak flow variability" at a review this comes back to history taking and patients as individuals. To suggest it for everyone at every review loses its credibility and risks yet another box ticking exercise. The Spirometry and Lung function section recommendations re spirometry appears to be	evidence on PEF variability. It is true there is a useful body of evidence around this, but that evidence suggests that it is not a very sensitive test in the diagnosis of asthma, and that it is of debatable value in the routine monitoring of asthma.

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				underpinned by low quality evidence. Interestingly the one element that has strong evidence to underpin it is the use of serial peak flow and yet this is considered not worthy of a recommendation. The ongoing discussion in the world of spirometry about the use of the fixed ratio to diagnose airflow instruction brings into question the whole discussion about diagnosing airflow obstruction in those who may have asthma and therefore by definition will be normal one day (ratio above or below 0.7) and abnormal the next.	
Education for Health	Full	1.1.10		This is already the cause of much debate. The issue of reversibility 12% and an increase in volume of 200ml is underpinned by poor quality evidence with studies that contain less than 1000 patients. We have just got the message across to primary care that 400mls in FEV1 and or return to normal lung function could indicate asthma so to change this back to 200mls and 12% is a massive retrograde step. Add to this the issue about 100mls vs 150 mls inter test repeatability then how can 200 mls be indicative of asthma? 200 mls could in reality be a 50 ml improvement and could be indicative of poorly performed spirometry by untrained health care professionals.	Thank you for your comment. Only one of the studies we identified used a cut-off of 400mls. In that study this was inferior to a cut-off of 200mls. It is regrettable that this runs counter to recent advice, but it is where the evidence takes us. The issue of inter-manoeuvre spirometry repeatability will have been part of the measurement "noise" in the reversibility studies we considered.
Education for Health	Full	1.1.16		Most people / practices do not have access to FeNO testing as the costs are prohibitive. To add FeNO to the diagnosis of which there is still	Thank you for your comment. The NICE Implementation team will produce support materials to facilitate uptake of the guideline into clinical

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				controversy over its evidence is not going to be possible or desirable If we think Spirometry is hard to do within a 20 minute consultation then to add in FeNO (and the guidelines insist it is obstructive spirometry AND FeNO or spirometry and reversibility primary care will collapse.	practice. The GDG acknowledges that FeNO testing in primary care is new and will require some initial investment. However, the best available evidence supports the clinical and cost effectiveness of FeNO and therefore the GDG considered the initial investment worthwhile for long-term patient health gains. FeNO is an extremely simple test to perform, it can be done in primary care, and in the long run should make management of asthma less rather than more difficult.
Education for Health	Full	1.2.9 1.2.10		FeNO test is not readily available in Primary care largely due to costs, which include equipment, servicing, maintenance, consumables and training. Furthermore, evidence does not appears not to be overwhelming the consultation actually states **"may help**" in the diagnosis and management of asthma. FeNO challenge testing requires new equipment, education and training. The introduction of the new medical contract in 2004 and QoF recommendation of measuring spirometry in all patients with COPD resulted in an influx of untrained staff doing poor quality spirometry and consequently poor diagnosis.	Thank you for your comment. The NICE Implementation team will produce support materials to facilitate uptake of the guideline into clinical practice. The GDG acknowledges that FeNO testing in primary care is new and will require some initial investment. However, the best available evidence supports the clinical and cost effectiveness of FeNO and therefore the GDG considered the initial investment worthwhile for long-term patient health gains. FeNO is an extremely simple test to perform, it can be done in primary care, and in the long run

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					should make management of asthma less rather than more difficult.
Education for Health	Full	1.2.12 1.2.13		This is totally inappropriate and unmanageable - Even in secondary care. Currently Bronchial Challenge testing would result in a secondary referral which not all centres provide. Either way increasing pressures on secondary care and waiting times would impact on a delayed diagnosis. This is also being advocated in a current political climate of reducing referral rates, so without a specialist interest education and insight into asthma and the purpose of bronchial challenge testing, how realistic is the guidance?	Thank you for your comment. A minority of those with suspected asthma will require bronchial challenge tests. We agree that bronchial challenge testing currently needs to be performed in secondary care, and this is stated in the 'linking evidence to recommendations' section of this chapter. Currently bronchial challenge testing is available in secondary care but the GDG acknowledges that this service provision is not widespread, although hospitals with a lung function laboratory should be able to perform challenge tests. The GDG acknowledges that patients in some areas of the country may need to travel to undertake a bronchial challenge test. The key point is that this is the test with the best combination of sensitivity and specificity, and it is widely used in other countries. The GDG did not feel that it should be denied to patients here.
Education for Health	Full	1.2.1		5 years is somewhat young would consider that this is 8 years. Spirometry in young children 5-8 yrs. is so very difficult. If this is used the paediatric population will yet again be disadvantaged, bearing in mind that most asthma is diagnosed in childhood and managed in	Thank you for your comment. The GDG acknowledges that there is a paucity of diagnostic test accuracy data in children and hence made a high priority research recommendation to elucidate the best diagnostic pathway.

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				primary care.	Furthermore, the GDG has added a caveat to the diagnostic algorithm for children to account for those children who are unable to perform objective tests from age 5 onwards that the principles in recommendation 1.2.1 should be followed until the child is old enough to perform objective tests adequately.
Education for Health	Full	1.3.2		These need to be made more easily accessible. These can easily be incorporated into systems and we suspect those health care professionals with education and knowledge will already have such systems in place. The challenge is to standardise practice not only in the use of the a validated questionnaire but how to interoperate them into a meaningful outcome for the patient.	Thank you for your comment. Accessibility to validated questionnaires is outside the remit of this guideline and will be referred to the NICE implementation team to consider when producing support materials to facilitate uptake of the guideline.
Education for Health	Full	1.3.3		PEFR variability is down to the patient doing the readings with all of the issues that presents. Also five years is too young.	Thank you for your comment. The GDG is aware of the limitations of self-reporting and hence placed PEFv in the diagnostic pathway accordingly. Objective tests are not recommended in children under 5 please see recommendation 1.2.1.
Education for Health	Full	1.3.7		Baverstock and other research on poor inhaler technique of HCPs shows more investment in training needed. It should be undertaken every time they are seen by a HCP. Monitor the inhaler technique of people with asthma after every asthma attack - when the device is changed - at every annual review. How about add on prescription collection and prescription delivery to the	Thank you for your comment. The GDG does not have the remit to control investment in training.

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				housebound who already have limited access to a health care professional and invest in training HCPs.	
Education for Health	Full	1.1.2		This is at odds with current guidance so rationale for change needed. If 30% of people are incorrectly diagnosed were the old guidelines actually being used? Still means 70% were diagnosed correctly and some of the 30% had asthma at the time. The recognition in the draft guidelines of the fact that even a small degree of reversibility needs consideration for treating with an ICS is to be applauded. Too often reversible airways disease is left untreated 'because it is COPD' and the patient is left at risk. We are concerned that there appears to be little understanding or appreciation of the real world about the impact on primary care. The use of Probability is still not fully embedded in the diagnosis of asthma, it has the potential to have a much greater impact if use was widespread. Education and training will be a major issue and time constraints – big concerns to the frontline HCP's nationwide The evidence as outlined in the tables appears to be very weak. This cannot surely help diagnose asthma by making it more complicated and costly. In the cost section it has been calculated as diagnosis time with appointment times for spirometry of 10-15	Thank you. This comment makes numerous points, but we believe they have been answered in the earlier responses of the developers to Education for Health. With regards to your queries about the costs, the cost of practice nurse time was taken from the PSSRU and is the most robust data we have concerning staff costing. With regards to the cost of bronchodilator reversibility, as this test appears in a pathway, we aimed to cost the incremental cost of performing the test as opposed to the stand alone cost. In the pathway a spirometry would have already been conducted once the individual is offered a bronchodilator reversibility test and therefore the cost of this will have already been taken into account at this point.

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				minutes at 73p per minute 7.30 for 10 minutes and therefore 43.80 per hour (not sure we would agree with that calculation. More importantly you have quoted bacterial filters at 99p per time (which is rarely used in primary care) The cost for the bronchodilator test has been set at £17.35-23.92 for the time to administer drugs but does not include time for spirometry as it says the first test will have already been done so the cost in reality is that cost plus spirometry cost of £9.49-13.14 plus FeNO.	
Faculty of Pharmaceutical Medicine	Full	General	General	This is a welcome and very thorough piece of work. It covers diagnosis and monitoring of asthma in adults and children, but specifically excludes consideration of treatment, and of severe/difficult asthma.	Thank you for your comment.
Faculty of Pharmaceutical Medicine	Full	General	General	It is disappointing to note that the quality of most of the evidence reviewed for this guideline was graded 'very low' to 'moderate' – very few studies were graded 'high'.	Thank you for your comment.
Faculty of Pharmaceutical Medicine	Full	General	General	It is disappointing to note that NICE does not appear to have collaborated with British Thoracic Society or with one of the other academic, professional or patient advocacy groups and support existing guidelines. The profusion of guidelines is likely to create confusion in clinical practice.	Thank you for your comment. The GDG does not feel that the recommendations on diagnosis in the NICE guideline are vastly different from that of BTS/SIGN. The NICE guideline provides more detail of when to perform certain objective tests. The only major difference is around FeNO testing. However, the section on FeNO in the BTS/SIGN

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					guideline was not updated in the 2014 update (the diagnosis chapter was last updated in 2011). The NICE guideline provides the most recent review of the FeNO evidence. It is possible that when BTS/SIGN undertake a formal review of diagnosis the recommendations may be more positive regarding FeNO for diagnosis.
Faculty of Pharmaceutical Medicine	Full	13	3	The guideline implies that asthma attacks and exacerbations are synonymous. However, we believe that attack and exacerbation are not synonymous and that this should be clarified. To most clinicians an attack is a sudden onset of wheeze often with an obvious precipitant e.g exercise, exposure to known allergen, which is often short-lived, resolving spontaneously or in response to a bronchodilator. An exacerbation may develop from a non-resolving attack, but often comes on insidiously over several days of declining peak flow, and leads to an increase in medication (including oral steroids) and presentation to a doctor (as stated elsewhere in the guideline e.g. page 192).	Thank you for your comment. In the context of this guideline asthma attack and asthma exacerbation are synonymous and the GDG has made this clear in the guideline.
Faculty of Pharmaceutical Medicine	Full	13	14	It is stated that there is "no gold standard test" to diagnose asthma. 15% period variability or bronchodilator response has been used as "definitive diagnostic test" for some time. Is that no longer considered the case?	Thank you for your comment. 15% variability has been used by some but has never been widely accepted, still less validated as definitive. The GDG defined the reference standard as physician diagnosis plus an objective test.
Faculty of	Full	13	31	FeNO is not practical in general practice where the	Thank you for your comment. The primary aim of

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Pharmaceutical Medicine				majority of asthmatics are diagnosed and managed. GPs have for 20 years been using PEF and symptom diaries on a daily basis for clarifying diagnosis and managing disease. Blood and skin prick tests are not useful or practical in general practice, neither are challenge testing with methacholine, histamine, mannitol, AMP or other provocative agents. In summary, the recommendations for diagnosis of asthma are that all subjects with symptoms suggesting asthma should have spirometry and measurement of FeNO; if spirometry shows an obstructive picture then bronchodilator responsiveness should be measured, if not then a methacholine challenge test should be offered. However, this assumes that all general practices have spirometers (which is not the case), and the guideline actually states that measurements of FeNO 'can be performed within primary care'; perhaps so, but how many practices possess the apparatus and expertise to do so? We predict that GPs following this guidance would create a large increase in the requests for methacholine challenge testing. Even if spirometry, reversibility, and FeNO could all be assessed in primary care, methacholine challenge testing would require referral to secondary/tertiary care. This seems to be imposing a large burden on both primary and secondary care. Was consideration be	this clinical guideline was to produce the most clinically and cost effective way to diagnose asthma accurately. The GDG acknowledge that the implementation of some objective tests in primary care will require initial investment and training. However, the health gains and improvements in patient outcomes have been shown to be clinically effective as well as cost effective for the NHS; please see the health economic analysis in appendix M. The NICE Implementation team will produce support materials to facilitate uptake of the guideline into clinical practice. Furthermore, the GDG do not consider that all of the recommendations are new to clinical practice, for example, spirometry services should be available in all GP practices already. The only new objective test recommended in the guideline is a FeNO test, however, the GDG consider that performing a FeNO test is much easier than performing spirometry. FeNO has been shown to be cost effective by both the original health economic model developed as part of this guideline's cost effectiveness analysis and by the NICE DAP health economic model. Currently bronchial challenge testing is available in

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				given at least to using Peak Flow both for initial screening for asthma (in conjunction with history & physical examination) and for reversibility testing?	secondary care but the GDG acknowledge that this service provision is not widespread. Hospitals with a lung function laboratory should be able to perform challenge tests. The GDG acknowledge that patients in some areas of the country may need to travel to undertake a bronchial challenge test. The current coverage is unknown however if there is more demand in future this service provision will become more widely available.
Faculty of Pharmaceutical Medicine	Full	22	3.2.1 and 3.2.2	Searching for evidence – this appears to repeat what has already been done by the Cochrane Airway group and we would question the need to repeat this exercise. However, we believe that the health economic literature search, described in section 3.2.2, is probably not duplicating other work and was a worthwhile exercise to undertake.	Thank you for your comment. The guideline follows standard NICE methodology for evidence-based clinical guideline development. We are aware that the Cochrane Airways Group have compiled an RCT database, but this is not the approach taken in the development of NICE guidelines. A literature search is performed for each individual review question within the guideline. Where Cochrane reviews are identified which match the systematic review protocol for that question, we look to see if the Cochrane review can be updated and therefore, the Cochrane literature search used also.
Faculty of Pharmaceutical Medicine	Full	95	12.1	Implicit in section 12.1 is that if obstruction is present on spirometry, then reversibility testing is performed at that visit, rather than a later date. This is not quite clear from the main guidelines summary, it does have practical implications; GPs need to ensure that their practice	Thank you for your comment. It may be possible to perform opportunistic spirometry when a patient first presents with symptoms. If this is not possible then we agree it would be sensible to make provision for reversibility testing by the practice nurse when

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				nurses are able to go on to perform reversibility testing (including administering salbutamol) if obstruction is found.	attending specifically for spirometry measurement.
Faculty of Pharmaceutical Medicine	Full	95	12.1	Section 12.1 states that 'The first step in interpreting any bronchodilator test is to determine if any change greater than random variation has occurred'. The threshold for a positive reversibility result is an improvement of 12% and 200ml for patients aged 16 and over; but 12% alone in the under 16s. Where the baseline FEV1 is small (e.g. 5 year olds) then 12% of that may be little more than 100 ml, but ATS/ERS guidelines require that the highest two FEV1 values of a set of manoeuvres agree by 100 ml to be considered repeatable (in such cases). Hence the effective 'measurement error' of a set of manoeuvres may be similar to the threshold for a positive reversibility result. This is an unavoidable difficulty. However the guideline fails to admit that distinguishing between moderate bronchodilator responses (say 12-15%) and random variation due to such measurement error is, inevitably, more difficult in small children.	Thank you for your comment. The GDG agrees that moderate bronchodilator response in the younger children may be difficult to detect because of the inherent variability of the test. This is why the algorithm does not rely on a single measurement as a diagnostic test, instead uses a combination of tests to make a diagnosis of airway obstruction.
Faculty of Pharmaceutical Medicine	Full	100	29	The unit cost of spirometry equipment to test for reversibility is given as £2.20 – we are unclear what this means or how it is derived. It seems to be only a fraction of what clinical research sites charge – about £120 – for performing spirometry, which takes into account capital	Thank you for your comment. The derivation of this cost and references are presented in the full economic write-up; please see appendix M cost-effectiveness analysis. The cost used in the guideline includes capital costs, healthcare

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				equipment costs, consumables and staff time to perform test and interpret results.	professional time and overheads. It is worth noting the cost in the report is for a single spirometry in the context of an asthma diagnosis, other spirometry costs in the literature are usually part of a comprehensive assessment of the patient carried out by a specialist in a specialist setting resulting in a much higher cost.
Faculty of Pharmaceutical Medicine	Full	212 - 213		The recommendations for monitoring the disease include administering a formal questionnaire e.g the ACQ, and measuring lung function, at every asthma review. The lung function measure can be FEV1, or Peak Flow - variability (stated on page 212) but just Peak Flow (stated on page 213) – which is to be recommended?	Thank you for your comment. We cannot find the anomalous statement. The actual recommendation (as opposed to any supporting text) clearly offers a choice between FEV1 and PEF monitoring.
Faculty of Sport and Exercise Medicine	Full	General	General	It should be made clear how the current draft guideline on diagnosis and monitoring relates to the regularly updated SIGN British Asthma Guideline. Whereas the present draft guideline offers a more definitive approach the latter provides a more probabilistic approach with advice to refer to specialist opinion in doubtful cases and where all the more objective diagnostic tests and procedures such as bronchial challenge and FeNO should be available. The present draft guideline provides valuable advice and makes a strong case for a wider application of such tests and would be more likely to be taken up in secondary rather than primary care.	Thank you for your comment. The GDG does not feel that the recommendations on diagnosis in the NICE guideline are vastly different from that of BTS/SIGN. The NICE guideline provides more detail of when to perform certain objective tests. Intra-person variability is an issue with most diagnostic tests, and will account for some of the imprecision in formal studies of sensitivity and specificity. The tests recommended in the guidance appear to have value despite this.

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				The strength of the present draft guideline is its focus on diagnostic precision and in this context the algorithms are useful . However the present draft guideline does not appear to take into account the intra individual variability of tests such as BHR and FeNO and unlike the BAG has nothing to say on prognosis , the latter being a particular concern of parents of newly diagnosed young patients.	Prognosis was not prioritised for inclusion in this guideline after stakeholder consultation.
Faculty of Sport and Exercise Medicine	Full	General	General	A strong case is made for the wider application of tests such as BHR and FeNO but in the absence of direct access to these how should clinicians proceed ? FeNO figures prominently in the present draft but does not appear in the 2014 BAG presumably because this was considered to be available to those patients referred to secondary care. Indeed in the 2104 BAG it is stated that "FeNO is limited to a few centres and more research is needed to be done before any recommendations can be made"	Thank you for your comment. The section on FeNO in the BTS/SIGN guideline was not updated in the 2014 update (the diagnosis chapter was last updated in 2011). The NICE guideline provides the most recent review of the FeNO evidence.
Faculty of Sport and Exercise Medicine	Full	51	7	Children <5yrs can perform objective tests as long as skilled staff are available . The statement here conflicts with comment on p 103 that BDR are "not able to be performed well " in this young age group - however they would be unlikely to be attempted in the primary care setting.	Thank you for your comment. Objective tests are not recommended in children under 5 please see recommendation 1.2.1.
Faculty of Sport and	Full	104 +		Review question 13.2 relates to PEF variability and yet in the following recommendations from p 109 FeNO	Thank you for your comment. The recommendations are not intended to be read in isolation and the

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Exercise Medicine				figures prominently in advance of the subsequent section on FeNO.	sequence of tests are conditionally dependent. Please refer to the diagnostic algorithms.
Faculty of Sport and Exercise Medicine	Full	General	General	In relation to point 4 above and to the assessment of BHR might it be easier to follow if after each individual test has been reviewed that the different algorithms are constructed and assessed for their clinical accuracy and health economic benefits ?	Thank you for your comment. The diagnostic algorithms provide the most clinically and cost effective way to diagnose asthma.
Faculty of Sport and Exercise Medicine	Full	General	General	The BAG 2014 suggest a cut off of 25ppb rather than the 40 in the present draft guideline . With the widespread use of and reputation of BAG with clinicians could the proposed central role of FeNO in the present draft cause confusion and controversy?	Thank you for your comment. Please see section 16.6 of the full guideline which provides the GDG's rationale for the diagnostic cut-off values chosen for FeNO.
Group of Occupational Respiratory Disease Specialists	Full	General		We were delighted to see that the importance of considering an occupational cause for asthma, and making an early specialist referral are highlighted throughout the document.	Thank you for your comment.
HQT Diagnostics	Full	General	General	Asthma attacks have been shown to reduce by 50% if Vitamin D level is increased Suggest GP tests Vitamin D and supplements so that 25(OH)D is between 100-150 nmol/L. Re-test after 3 months	Thank you. Therapy for prevention of asthma attacks is important, but this guideline is about diagnosis and monitoring, not treatment.

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				There is a review of the evidence at: http://vitamindwiki.com/Overview+Asthma+and+Vitamin+D	
HQT Diagnostics	Full	General	General	Inflammation is a major factor in Asthma. Suggest GP tests for Fatty Acids and supplements to achieve: • **Omega-3 Index: >8%** • **Omega-6/3 Ratio: <3:1** This is done by increasing the amount of Omega-3 and reducing the amount of Omega-6 Suggest re-test after 3 months More at: http://ajcn.nutrition.org/content/65/4/1011.full.pdf+html http://www.ncbi.nlm.nih.gov/pubmed/25149823 http://www.sciencedirect.com/science/article/pi	Thank you. Therapy for prevention of asthma attacks is important, but this guideline is about diagnosis and monitoring, not treatment.

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				i/S1388198114001656 www.hqt-diagnostics.com	
HQT Diagnostics	Full	General	General	Refer patient to registered Dietitian or Nutritional Therapist for advice about Diet and Lifestyle (www.bda.uk.com or www.bant.org.uk) For a review of how diet and lifestyle is relevant: http://jdmoyer.com/2010/07/17/how-i-cured-my-asthma-with-one-simple-lifestyle-change/	Thank you for your comment. Diet and lifestyle advice in the diagnosis and monitoring of asthma was outside scope.
Leeds Teaching Hospitals NHS Trust	Full	General		The Yorkshire Asthma Network (YAN) is a collaborative group of secondary and tertiary care physicians and nurses from the hospitals in North, South and West Yorkshire. It meets four times a year to discuss developments in asthma, to discuss cases under consideration for biologic/cytotoxic medication and for continuing education. Our response to the guideline is directed at the sections concerning adult asthma only. The YAN recognised that the aim of the NICE guideline	Thank you for your comment.

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				was to "determine the most clinical and cost-effective way to effectively diagnose people with asthma and determine the most effective monitoring strategy to ensure optimum asthma control." We also appreciate that incorrect diagnosis is a significant problem and that the guideline is aimed at primary, secondary and community-based settings. We feel that applicability of this guideline to primary and community-based settings is vital given that the vast burden of asthma is centred here.	
Leeds Teaching Hospitals NHS Trust	Full	General		We feel that the emphasis in the guideline is wrong and that there needs to be much more of an emphasis on getting the basics right. There is not enough on history, examination, personalised action plans and achieving accurate spirometry, as well as interpreting it correctly. These are all vital to the primary care assessment of the patient at first presentation.	Thank you for your comment. The aim of the guideline is to provide the most clinically and cost effective way to diagnose asthma accurately. Recommendation 1 clearly states that a structured history should be taken and a physical exam performed. Competence in performing history and examination are tested at medical school and in post-graduate examinations, and are beyond the remit of this guideline. Guidance to ensure the proper performance of the objective tests is outside the remit of this guideline and are available from other sources. Excellent guidance on performing a spirometry test is provided by ARTP.

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					PAAPs are outside the scope of this guideline as these are part of asthma management.
Leeds Teaching Hospitals NHS Trust	Full	General		A considerable number of asthmatics are poorly compliant and cannot use their inhalers properly. One of the main findings from the National Review of Asthma Deaths was the need to check inhaler technique, to check prescription records and in providing written management information. These issues are not mentioned enough in the guideline and should be more prominent as they have significant clinical and economic consequences if not done well.	Thank you for your comment. We agree that inhaler technique and adherence to medication are important, and they are covered. Please see chapters 28 and 29 on monitoring adherence to treatment and on monitoring inhaler technique. Guidance on asthma management is outside the remit of this guideline.
Leeds Teaching Hospitals NHS Trust	Full	General		It was disappointing that the development group had such little representation from adult primary care given the target audience of this guideline. Furthermore, we have considerable concern that there are already a number of guidelines available. How will this complex, unwieldy and at times conflicting guideline fit in? How will a busy General Practitioner prioritise which guideline to use?	Thank you for your comment. There are two GP members and a primary care nurse practitioner on the GDG. The guideline covers people of all ages and hence required both paediatric and adult physician input as well as that from primary care. The size of the group is thus a compromise between the need to cover all these viewpoints and the risk of making the group excessively large and unwieldy. Furthermore, stakeholders were consulted on the GDG composition at the start of guideline development.

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					The GDG disagrees that the implementation of the diagnostic algorithm is prohibitively complex. Patients who present to their GP with mild symptoms of asthma can perform spirometry, BDR and FeNO tests during a follow-up appointment with the practice nurse to get a positive diagnosis of asthma. A small proportion of patients with diagnostic uncertainty will go through the longer route in the diagnostic pathway in order to obtain further objective testing evidence of asthma. The GDG considered that patients with intermittent symptoms should be called back for further review.
Leeds Teaching Hospitals NHS Trust	Full	General		We do not feel that this guideline will improve the huge variation in the standards of care because it focuses too much on specialised tests.	Thank you for your comment. The only specialised test recommended in the diagnostic pathway is bronchial challenge, which will be required by a minority of those with suspected asthma. Spirometry measurement, bronchodilator reversibility and serial PEF recordings are all used already in Primary care. FeNO is new, but it is easy to perform.
Leeds Teaching Hospitals NHS Trust	NICE	15	1.1.10	Bronchodilator reversibility This guideline adds more confusion to the definition of reversibility. Until last year, BTS/SIGN had suggested 200mls or greater was significant, which confused many in primary care as this conflicted with the NICE COPD guideline. The latest version of the BTS/SIGN guideline is now in line with the NICE COPD guideline where	Thank you for your comment. Neither the BTS/SIGN nor NICE COPD guideline makes a firm recommendation on the basis of a positive test. The more reversible the more evidence there is of asthma. The evidence reviewed in this guideline supports the thresholds specified in the recommendation; please see chapter 12. BDR does

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				significant change is 400mls or greater. This consultation document therefore appears to contradict other published NICE guidance.	not have 100% sensitivity and specificity.
Leeds Teaching Hospitals NHS Trust	NICE	16	1.1.12 and 1.1.13	Peak flow variability as part of diagnosis We feel that the inclusion of this in the diagnostic algorithm is a retrograde step. PEF sensitivity for the diagnosis of asthma is low and is a cumbersome exercise for patients. We feel that it is seldom useful.	Thank you for your comment. The use of PEFv has been strongly supported by primary care and was shown to have a very high specificity in the evidence review; please see chapter 13.
Leeds Teaching Hospitals NHS Trust	NICE	17	1.1.16	Fractional Exhaled Nitric Oxide (FENO) In the preamble to the guideline, the authors themselves noted that there is uncertainty about the sensitivity and specificity of FENO and yet it features significantly in the guideline as an established test. Furthermore clinical trials have demonstrated variable results using FENO in diagnosis and management. Some studies suggest it correlates less well with pulmonary eosinophilia than some other biomarkers. FENO is less good as a biomarker of treatment response, though high FENOs are useful to potentially highlight poor compliance.	Thank you for your comment. The clinical introduction sets the scene for why the review question was asked – to undertake a systematic review of the diagnostic test accuracy of FeNO and other objective tests under review. The evidence review provides the data on sensitivity and specificity of each objective test under review.
Leeds Teaching Hospitals NHS Trust	NICE	17	1.1.16	Fractional Exhaled Nitric Oxide (FENO) Some areas of the quite complex algorithms seem unnecessary. Does the guideline group really want someone with obstructive spirometry, reversibility and presumably an appropriate history to have a subsequent FENO as part of diagnostic proof?	Thank you for your comment. Yes that is correct; the recommendations say that someone with obstructive spirometry, reversibility and an appropriate history to have a subsequent FENO as part of diagnostic proof. The GDG took the view that the two test different aspects of asthma, that the diagnosis is

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					more secure if both are done, and that this a cost-effective combination. They noted that a FeNO test takes less than 5 minutes to do.
Leeds Teaching Hospitals NHS Trust	NICE	17	1.1.16	Fractional Exhaled Nitric Oxide (FENO) In the cost analysis, there does not appear to be an account of the cost of a FENO meter, where-as there is in the cost of spirometry.	Thank you for your comment. The cost of a FeNO meter was included in the analysis. This was taken from: Harnan S, Tappenden P, Essat M, Gomersall T, Minton J, Wong R et al. Measurement of exhaled nitric oxide concentration in asthma - NIOX MINO and NObreath, 2013. Available from: http://guidance.nice.org.uk/DT/13 *(Guideline Ref ID DG13)* This analysis calculated the upfront cost of the equipment and the number of times it could be used before replacement to calculate the per-patient cost.
Leeds Teaching Hospitals NHS Trust	NICE	16	1.1.15	Peripheral eosinophilia, IgE and RAST We were surprised about how negative the views with regards to these relatively inexpensive tests were. It is becoming increasingly important to phenotype asthmatics so that treatment can be tailored to the individual. New biologics are available or in development that target allergic asthma and/or eosinophilic asthma. Neutrophilic asthma, asthma with COPD overlap or asthma with chronic infection will need	Thank you for your comment. The GDG agrees that these tests can be important in the phenotyping of people with a confirmed diagnosis of asthma, although they also note that with currently available treatment for non-severe asthma this is generally not necessary for management purposes. However, the diagnostic accuracy of peripheral blood eosinophils, serum IgE tests to make the initial diagnosis of asthma, as opposed to guiding subsequent

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				alternative directed interventions. Not categorising patients appropriately could have significant clinical and economic consequences. We believe that the presence of atopy or eosinophilia in the context of a good history provides support for eosinophilic inflammation being present. Whilst not a diagnostic test, for a disease where diagnosis is often clinical, it is a helpful and relatively inexpensive test.	treatment, was not supported in the review of the best available evidence; please see chapters 17 and 15 for the evidence review.
Leeds Teaching Hospitals NHS Trust	NICE	17-18	1.1.19-1.1.21	Airway hyper-responsiveness The current ability for primary care to test for airway hyper-responsiveness is even less than for FENO. Furthermore, it is uncertain how many General Practitioners know about this test. There appears to be an over-emphasis for the need for this in a guideline that is aimed at the diagnosis of most asthma, which is in primary care. More specifically about different tests for airway hyper-responsiveness: It should be noted that histamine is not licensed to test for airway hyper-responsiveness in the UK, instead it is only available as Ceplene(R) injection, which is licensed to treat AML. Consequently using inhaled histamine in the UK using a licensed product represents an off-label use via an unlicensed route of administration. NICE	Thank you for your comments. Patients who present to their GP with mild symptoms of asthma can perform spirometry, BDR and FeNO tests during a follow-up appointment with the practice nurse to get a positive diagnosis of asthma. A small proportion of patients with diagnostic uncertainty will be referred to secondary care for bronchial challenge testing and go through the longer route in the diagnostic pathway in order to obtain further objective testing evidence of asthma. Therefore, the GDG disagrees that there is 'an over-emphasis for the need for this in a guideline'; most people with asthma will be diagnosed in primary care, but a few people with diagnostic uncertainty will be referred to secondary care. The GDG agrees that methacholine is also used off label and this agent has been included in the recommendation footnote.

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				should clearly state this within the guideline. As methacholine and histamine are unlicensed medicines, obtaining pharmaceutical grade stock can be problematic. NICE should clearly state reliable sources of pharmaceutical grade stock to perform these tests. Furthermore, most hospitals do not currently have the equipment required to perform airway hyper-responsiveness testing using methacholine or histamine, and this should be considered as a challenge to implementation. How can this take such a prominent place in the diagnostic algorithm where realistically it is only available in research units? The complexity of airway hyper-responsiveness testing using unlicensed preparations such as methacholine or histamine has not been considered adequately, as these products may need to be serially diluted to perform the test (depending on the source of methacholine or histamine obtained), which can bring errors into the test due to dose miscalculation. Mannitol is not subject to dosing errors, which is an advantage of this preparation is licensed and more widely used. Due to the variation in dose and concentrations available for methacholine and histamine as unlicensed	The GDG accept that few GPs are familiar with bronchial challenge testing, and that availability in secondary care is not universal. However, it is the single test with the best combination of sensitivity and specificity for diagnosis of asthma, and the GDG therefore concluded that it should be more widely used in this country. Regarding histamine being off-label for bronchial challenge test, the GDG agrees with this and has included histamine in the off-label footnote. Guidance on procurement of agents such as methacholine and histamine is outside the remit of NICE clinical guidelines. However, we will refer this issue to the NICE Implementation team to possibly be supported via the support materials they produce. Regarding challenge testing with mannitol, please see chapter 19; the review of best available evidence did not support a recommendation for indirect challenge testing with mannitol but the GDG made future research recommendations to investigate the utility of mannitol challenge tests in both children and adults.

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				medicines, there is a lack of standardisation of practice, which was also highlighted by the lack of consistency of study methods reported in the NICE guideline. NICE should consider recommending a standardised approach to direct airway hyper-responsiveness testing if it is going to pursue these in its algorithm. The literature used to inform section 19 - Diagnosis: Indirect bronchial challenge test with mannitol, is incomplete. The guideline fails to include data from Koskela et al Chest 2003;124:2171-7 (which is used to provide data in section 18 - histamine challenge tests, and so would appear unusual to include for one clinical evaluation but not the other), and from Brannon et al. (Respiratory Research 2005;6:144 http://respiratory-research.com/content/6/1/144 - a Phase 3 study including 654 people aged 6 years and over reporting a sensitivity and specificity for mannitol of 88.7% and 95.0% in subjects not taking ICS). This latter study was not specifically excluded in the Appendices document.	Regarding the references referred to, the Brannan 2005 paper was excluded due to the population. The study recruits asthmatics and non-asthmatics, rather than the protocol population of suspected asthma with respiratory symptoms. In the study, non-asthmatics were required never to have had a clinical diagnosis of asthma or experienced signs and symptoms suggestive of asthma. Studies of this design were excluded as they do not represent the population in which the test will be used clinically (people with respiratory symptoms) and inclusion of healthy controls may lead to over estimations of specificity. This paper was excluded during the first sift and therefore, does not appear in the excluded studies list. Koskela 2003 was excluded as it does not evaluate the diagnostic accuracy of mannitol for a diagnosis of asthma made by the reference standard, in the review population of people with suspected asthma. This study assesses the agreement between tests in people with already diagnosed asthma. We agree that the study was included in the review of the diagnostic of methacholine/histamine. However, this evidence was not used in decision making by the GDG, as it only provides the accuracy of histamine

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					to predict a positive mannitol test in people with asthma. It does not provide the accuracy of histamine for the diagnosis of asthma in people with suspected asthma.
London Respiratory Network	Full	86, 95	General	**Spirometry and bronchodilator reversibility** One strikingly significant change to practice is the recommendation for mandating spirometry with reversibility testing where an obstructive pattern is identified (1.1.9 in NICE guidline). The London Respiratory Network is absolutely committed to promoting high-quality spirometry when indicated: as the London Respiratory Team we contributed to the "Guide to Performing Quality Assured Diagnostic Spirometry" [1] and have promoted its use as a diagnostic test. It is unclear what the policy change is trying to accomplish? If the problem is diagnostic accuracy, then current practice in spirometry for diagnosis of COPD would suggest this is not a good solution. While general practice is capable of providing quality assured spirometry, it is certainly not universally available. There are already concerns over the quality and	Thank you for your comment. We agree that there are difficulties in providing quality-assured spirometry, but also agree that this is an extremely useful measurement not only in asthma but in COPD and other respiratory diseases. Optimal care of these patients includes the ability to access spirometry more readily, and the GDG did not feel that this guideline should compromise in that regard. The evidence base for using spirometry & reversibility is set out in chapters 10 and 11 of the full guideline. It is not recommended over history and examination as you suggest, but in conjunction.

[1] http://www.educationforhealth.org/data/files/resources/spirometry_guide_16-4-13.pdf

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				accuracy of spirometry currently performed, typically for COPD diagnosis, and the interpretation of the data. The Department of Health is preparing to issue a policy document requiring all clinicians performing spirometry to be ARTP or equivalent-qualified and an ongoing reaccreditation process for those with such qualifications. We are concerned that the greater costs and organisational challenges that are likely to be incurred in sourcing and providing the required training and supervision so that spirometry for both COPD and now all asthma diagnoses is performed by ARTP or equivalent-qualified clinicians have not been estimated and taken into account. We also note that the previous requirement for universal spirometry with reversibility testing for COPD diagnosis has now been removed from the Quality and Outcomes Framework for general practice and replaced with post-bronchodilator spirometry. In implementing this asthma guidance there is therefore potential for confusion as to which is the appropriate spirometry testing for which individual. There is a danger that those currently providing a spirometry service outside of a reaccreditation period will need to cease the service until such a time that they can complete an update. This could not only lead to a delay in diagnosis, and/or treatment for asthma if the	

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				diagnosis has to be based on spirometry with reversibility testing, but may also lead to an unwarranted increase in referrals to hospital respiratory departments. This is a major change from current practice, and it is not obvious from the evidence whether such patients would benefit from a respiratory assessment at this stage instead of the systematic application of the current strategies recommended in guidelines and used in clinical practice, that is, using (repeated) clinical history and examination supported by peak flow monitoring and response to trials of therapy, with the reservation of referral for further testing including possibly spirometry, FeNO testing and/or bronchial challenge testing, in cases of doubt or difficulty in diagnosis. The evidence base for recommending spirometry over (repeated) clinical history and examination supported by peak flow monitoring and response to trials of therapy strategies is lacking.	
London Respiratory Network	Full	130	General	**Fractional exhaled nitric oxide (FeNO)** We believe that the concept of introducing FeNO testing as standard (1.1.16 in NICE guideline) must be tested in some volunteer populations before implementation because:	Thank you for your comment. We agree that in an ideal world it would be useful to pilot all new guidance. However, NICE produces national recommendations to guide the best clinical practice on the basis of the best available evidence. NICE does not have a remit to arrange 'trials' of new standards of practice in volunteer populations.

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				- Whilst an argument is made for its cost-effectiveness, there needs to be more work investigating its cost based on the volume of use. The equipment costs are not insubstantial (about £3,000 for a machine) and, unlike tests like spirometry, the equipment costs of doing each test (without taking into account health professional time) are also not negligible at about £20 a test, and vary with the number of tests done over a period of time. Piloting in various settings with different populations and different numbers of tests over time is needed to inform the 'business case aimed at those responsible for commissioning and assessing the testing' referred to in the consultation document 'to support investment in new equipment and to provide education and training in its use for primary care professionals' before consideration can be given to introducing FeNO testing as standard. - Currently, and as acknowledged in the consultation document ('FeNO challenge testing has only recently been introduced in primary care, and the availability of FeNO testing equipment is patchy.'), FeNO is rarely used outside of hospital-based respiratory services. Even in hospital settings it is much more available for use in children's services and in tertiary care than in adult secondary care respiratory	The GDG acknowledges that FeNO testing in primary care is new and will require some initial investment. However, the best available evidence supports the clinical and cost effectiveness of FeNO and therefore the GDG considered the initial investment worthwhile for long-term patient health gains from increased accuracy in asthma diagnoses and reduced demand on NHS services, for example, preventable unscheduled healthcare utilisation. FeNO is an extremely simple test to perform and can be done in primary care. Trials of treatment are certainly used traditionally, but there is little formal evidence to support their use. We note that BTS/SIGN also found no good trial evidence and that the use of a trial of treatment is graded as a Good Practice Point for children and a Grade C recommendation for adults within that Guideline. A counter view is that they can lead to misdiagnosis when a natural improvement in symptoms coincides with, and is spuriously attributed to, introduction of asthma therapy. The proposed diagnostic sequence allows their use in cases of genuine doubt (see algorithms B1 & C) but encourages the use of more objective tests

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				services according to a poll of London colleagues. The LRN has concerns that the current lack of availability of FeNO testing may lead to inconsistencies of diagnosis across the country with practices 'picking and choosing' parts of the recommended algorithms that are available within their area. Conversely there is a further risk that practices following the algorithm without deviation would delay diagnosis whilst awaiting appointments in clinics able to offer FeNO testing. Although it is not unfeasible to suggest FeNO as a helpful tool in complex diagnoses in primary and secondary care, it seems at this time over-ambitious to introduce it as a national standard without prior testing of models of provision, and value added of such models. Settings using FeNO in this way are might include community or hospital breathlessness clinics or other hub and spoke models; - The LRN would like to know why FeNO testing is advised within the B1 algorithm following finding obstructive spirometry with positive reversibility and questions what the benefit of this added data would be in comparison to moving straight to a 'trial of treatment' a process commonly used, well understood and a mainstay of the discussion of diagnosis in the existing NICE-approved BTS/SIGN guideline. Similarly we don't understand why the B2 algorithm recommends FeNO	beforehand. The two instances of multiple testing which you question are a reflection of the imperfect diagnostic accuracy of the relevant tests. They have some utility as described in the full guideline, but the GDG felt that diagnosis would be more secure if both were performed. In both instances one of the tests is a FeNO measurement which can usually be obtained in 5 minutes or less. We agree that because the FeNO test can be affected by smoking status we have added a recommendation to reflect this. The prevalence of smoking in people with asthma is approximately 20% meaning that cigarette smoke will not affect the diagnostic accuracy of FeNO in 4 out of 5 people. This is a diagnostic guideline and smoking cessation is outside the remit of this guideline.

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				testing in patients with 'normal' spirometry but advises 4-6 week peak flow monitoring regardless of whether the FeNO test is negative or positive. - While we recognise the potential benefits of FeNO testing when there is diagnostic uncertainty, we were surprised to see that the algorithms and text do not include the importance of assessing smoking status as part of asthma diagnostic work-up, not only because the opportunity to intervene and support smoking cessation is lost, but because of the well-described impact of smoking on FeNO results (referenced and referred to in the Guideline). The Guideline Development Group notes that, "FeNO levels can be altered by corticosteroids, smoking or previous smoking history and diet. The GDG excluded studies in which more than 50% of the population were taking corticosteroids, or if the smoking history of the population was unclear". - This is a sizeable problem. According to the last national BTS audit, 1 in 3 adults admitted to hospital with asthma are current smokers. The effect of cannabis or other smoked drugs on results of FeNO testing is not clear but would potentially also affect the results of significant numbers of people. FeNO measurement in someone with asthma, without first having assessed	

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				smoking status, will not be an improvement; it may be inaccurate and will introduce waste into the system. We would strongly recommend that if FeNO testing is being considered, clinicians treating children and adults must first take a carbon monoxide (CO) reading, and manage the result of that, including enabling evidence-based smoking cessation, if the CO level is raised, before considering proceeding to a FeNO.	
London Respiratory Network	Full	247, 256	General	**Asthma Monitoring and Inhaler Technique, Asthma Self-Management Plans** As a group we feel that the importance of patient education and individualised support may have been understated throughout the guidelines. It is disappointing that the use of asthma action plans, both the development of them at diagnosis and the revision of them at annual reviews, is not emphasised. This is despite the recommendations made by the National Review of Asthma Deaths (NRAD) (May 2014). Furthermore, despite the overwhelming evidence that adherence is a significant problem, there is little emphasis on clinical skills in, and responsibility for, recognising non-adherence and supporting patient behaviour change. Instead, the onus for clinicians conducting reviews is placed on the gathering of	Thank you for your comment. We agree that action plans are important and should be employed as soon as diagnosis is established; these fall under asthma management which will be the subject of a following NICE guideline. We do not agree that recognising adherence is understated; the relevant evidence was considered and discussed in the full guideline, but unfortunately no clear recommendation on how to identify this emerged. We do not agree that collection of lung function data is emphasised at the expense of checking inhaler technique; both are subject of a single monitoring recommendation. Please note that NRAD was not published until the guideline scope was agreed, and most of the evidence reviewing completed.

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				numerical data from spirometry and peak flow readings. Monitoring and improving inhaler technique and use and smoking status/cessation advice are also likely to contribute more to long term asthma control and reduction of future respiratory disease. Implementing these investigations into annual asthma reviews would constitute a substantial addition to workload in general practice and the evidence cited for the recommendation to monitor numerical data is acknowledged as being of low quality and relevance. All the cited studies refer to the use of peak flow guided self management plans, not to health professional use of peak flow (or spirometry) data to monitor asthma control in follow up consultations. If numerical data were to be employed, there should be an improvement test to see whether the use of handheld micro-spirometry to monitor FEV1 at office visits could be of benefit because it is a quick and simple indicator of airflow obstruction and may have the dual advantage of identifying the risk of COPD in the smoking population. We would argue that the existing national guidance on asthma reviews is adequate, but implementation is inconsistent. Therefore the answer to "What are we trying to accomplish?" is surely better quality reviews, which require the implementation of evidence-based behaviour change	We agree that the evidence for monitoring FEV1 or PEF is not strong. The GDG debated this at some length and their deliberations are described in the full guideline; they took the view by consensus that measuring lung function is of value. We do not think that this need be in competition with any proven behaviour change interventions; both may be useful.

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				interventions, not more tests?	
Manchester University	algorithm			Algorithm is likely to be the most commonly used of the documents. Please insert a text box with the abbreviations used with their explanations.	Thank you for your comment. This change has been made.
Mid Yorkshire NHS Trust	Full	General		Firstly I wonder why 20% reversibility is needed when using the PEFR measure to confirm asthma whereas in the new guidance spirometry reversibility need only be 12% or 200mls? Secondly I would like to raise whether it is in fact feasible to do the recommended testing as availability of exhaled nitrous oxide measurement devices, at my place of work at least, are not commonly available especially not in a clinic setting. I am aware that the devices required come at quite a cost whilst many trusts are struggling financially anyway. Thirdly reversibility spirometry too is a difficult thing to achieve in all patients as it is well known that due to the variable nature of the disease asthma patients will sometimes blow normal spirometry. Often when I see patients in clinic they have suspected asthma and as the guidance recommends have been started on asthma medication. It would be unethical to stop this and let them deteriorate in order to do testing. Ideally	Thank you for your comment. The 20% figure for PEF variability is based on the variation between measurements made at home over a period of at least 7 days. The 12% reversibility in FEV1 is based on a "before and after bronchodilator" measurement made in 20-30 minutes at the surgery or hospital. They are therefore measuring different aspects of airway variability. The justification for the cut-offs chosen is in the relevant chapters of the full guideline. FeNO meters incur an initial expense but our cost-effectiveness analysis suggests that this is eminently worthwhile in terms of facilitating accurate diagnosis. The guideline acknowledges that many patients will not have obstructive spirometry at presentation, and there are therefore separate algorithms for those with and without obstruction (Algorithms B1 and B2).

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				spirometry would have to be done on initial presentation including reversibility and this is not always possible as patients can be too unwell and capacity to do so is not always available from the healthcare provider. In stable patients who have never had reversibility testing this new push to get a diagnosis could lead to normal spirometry and misinterpretation that the person therefore does not have asthma.	
Napp Pharmaceuticals	Both	General	General	We welcome the opportunity to comment on this draft guideline. We support improved diagnosis and better management of asthma. We are concerned however that there are a large number of guidelines and guidance documents, from a number of different sources, available for health care professionals (HCPs) who have an interest in managing asthma. Whilst the NHS struggles with budgets and HCPs with time pressures we are concerned that all of the excellent work and time involved in producing these guidelines will be of little practical use. We would encourage NICE to produce one overarching simplified document to cover, diagnosis, treatment and monitoring. The emphasis for HCPs has to be on better care to prevent deaths from asthma. We believe that there are two main areas that could be improved through monitoring; these	Thank you. The problem with one over-arching document for asthma would be its size and the time required to produce it. When the forthcoming NICE Asthma Management guideline is published the NICE pathway for diagnosis and monitoring will be combined with the management pathway.

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				are adherence and inhaler technique; improvements in both should help to reduce the number of admissions and ultimately deaths from asthma. Priority should be given for the continuation and ongoing development of outcome indicators for and relating to asthma to ensure that there is an adequate focus on asthma.	
Napp Pharmaceuticals	NICE	4		We agree that it is key to optimise asthma control with more effective monitoring but would recommend that NICE states that this should be in conjunction with medication reviews. This could utilise the existing community pharmacy contractual framework (tMURs and NMS). We believe that monitoring is important and that this should improve care by helping HCPs adjust treatment to provide the most appropriate dose of medicines (both up and down the BTS treatment ladder) in a cost effective way in line with NICE guidance *(e.g. TA138)*.	Thank you for your comment. Recommendation 1.3.1 has been expanded with bullet points if control is found to be suboptimal which encompass this suggestion.
Napp Pharmaceuticals	NICE	5		We are pleased that NICE has highlighted the importance of continuity of care when paediatric patients move to adult care systems. This should involve all HCPs along the treatment pathway from primary and specialist care including the invaluable role that community pharmacists could and should be able to	Thank you for your comment.

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				provide. Integrated care for patients with asthma is key to prevent patients slipping through the net. Communication channels between primary care, secondary care and community pharmacy may not currently be in place to support the patient. The transfer of care for patients who are being discharged from hospital is equally important. Ensuring that patients understand their medicines and how to take them effectively by utilising community pharmacy can prevent re-admissions. http://www.england.nhs.uk/wp-content/uploads/2014/08/psa-imp-saf-of-discharge.pdf Following this patient safety alert PrescQipp have produced a guide to support the implementation of a transfer of care service. http://www.prescqipp.info/newsfeed/the-prescqipp-transfer-of-care-webkit-is-live	
Napp Pharmaceuticals	NICE	8	Last line	Are there meant to be options here, the text is not clear? It states: *…"either a":* the text then goes to the top of page 9 and describes the FeNO levels but there is no *"or b":*	Thank you for your comment. The 'a' at the end of the sentence is intended to be the indefinite article and not letters 'a' and 'b' by which to differentiate the two options given over the page. The options following the colon are differentiated by dashes not letters. In reality the issue of widows and orphans will not be present in the web version of the NICE guideline.

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Napp Pharmaceuticals	NICE	8	General	The diagnostic tests recommended are ideal however we wonder how many GP practices have the relevant equipment and fully trained asthma nurses to carry out the tests and what the financial impact on the NHS would be to set up these services if they were not available currently.	Thank you for your comment. The primary aim of this clinical guideline was to produce the most clinically and cost effective way to diagnose asthma accurately. The GDG acknowledge that the implementation of some objective tests in primary care will require initial investment and training. However, the health gains and improvements in patient outcomes have been shown to be clinically effective as well as cost effective for the NHS; please see the health economic analysis in appendix M. The NICE Implementation team will produce support materials to facilitate uptake of the guideline into clinical practice.
Napp Pharmaceuticals	NICE	9	Monitoring asthma control	The first bullet point mentions the Asthma Control Questionnaire or Asthma Control Test. We would like to suggest that NICE includes the RCP 3 questions here. In the last month: • have you had difficulty sleeping because of your asthma symptoms (including cough)? (662P) • have you had your usual asthma symptoms during the day (cough, wheeze, chest tightness, or breathlessness)? (662Q) • has your asthma interfered with your usual activities (e.g. housework, work/school, etc.)? (662N).	Thank you for your comment. Please see chapter 23; the best available evidence did not support making a recommendation to use the RCP 3 questions to monitor asthma control. The GDG made a future research recommendation to investigate the clinical and cost effectiveness of the RCP 3 questions to monitor asthma control.

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Napp Pharmaceuticals	NICE	9	Monitoring asthma control	Third bullet point. After every asthma attack – seems a little unrealistic as it will not be possible to monitor outside of the care setting unless there is a HCP present. We would suggest modifying this to: *at every consultation relating to an asthma attack in all care settings.*	Thank you for your comment. We have made the suggested change.
Napp Pharmaceuticals	NICE	21	1.3.1	We suggest that this should also include: • Increase frequency of reviews following an attack • Ensure that a personal asthma action plan is in place and is reviewed (this last point is one of the key messages from the NRAD report[1]). 1. The NRAD Report was published by Royal College of Physicians RCP in 2014: Why asthma kills. The National Review of Asthma Deaths (NRAD) https://www.rcplondon.ac.uk/sites/default/files/why-asthma-still-kills-full-report.pdf	Thank you for your email. Guidance on frequency of reviews following an asthma attack and PAAPs are outside the scope of this guideline.
Napp Pharmaceuticals	NICE	21	1.3.2	As comment 6 above. Consider including the RCP 3 questions.	Thank you for your comment. Please see chapter 23; the best available evidence did not support making a recommendation to use the RCP 3 questions to monitor asthma control. The GDG

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					made a future research recommendation to investigate the clinical and cost effectiveness of the RCP 3 questions to monitor asthma control.
Napp Pharmaceuticals	NICE	21	1.3.7	We would suggest that NICE adds, either in this point or as a new point e.g. *1.3.8 Discuss adherence in particular if the person is / should be taking regular preventer therapy.* We believe that this point is particularly important and was highlighted in the recent NRAD report[1]: "There was evidence of under-prescribing of preventer medication. To comply with recommendations, most patients would usually need at least 12 preventer prescriptions per year. Among 168 patients on preventer inhalers at the time of death, either as stand-alone or in combination, the number of prescriptions was known for 128, and 49 of these (38%) were known to have been issued with fewer than four and 103 (80%) issued with fewer than 12 preventer inhalers in the previous year" 1. NRAD report: https://www.rcplondon.ac.uk/sites/default/files/why-asthma-still-kills-full-report.pdf (page x point	Thank you for your comment. The GDG has added bullet points to recommendation 1.3.1 to reflect this.
Napp Pharmaceu	NICE	21/22	1.3.7	We suggest that the community pharmacist should be included as part of the team monitoring both inhaler	Thank you for your comment. Guidance on service delivery is outside the remit of this guideline. The

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ticals				technique and adherence. There is also an opportunity to help through MUR and NMS: • In the diagnosis of a person's worsening asthma through monitoring the over use of rescue therapy. • Detection of inappropriate prescribing of LABA monotherapy. • Step up or down to the most appropriate dose.	recommendations focus on what should be done without specifying who might do it.
National Inhaler Group	NICE	1.3.7		It is pleasing to see that the draft guideline recognises the importance of inhaler technique as a key part of routine monitoring. However we are not entirely in agreement with the three situations you have identified. The Quality Standard for asthma recommends : *QS 4 - People with asthma are given specific training and assessment in inhaler technique before starting any new inhaler treatment.* What is the basis for these three situations having been selected? These do not appear to relate to the wording in the Quality standard. Inhaler technique should be checked at every opportunity when a healthcare professional sees a patient, not just in these three instances. It should also be explicit that this is not about asking a patient whether they can use an inhaler, but about asking the patient to	Thank you for your comment. The GDG did not feel able to recommend a check on inhaler technique every time a person picks up a new prescription for the same inhaler. There is no evidence that this is necessary. Regarding demonstrating inhaler technique, the GDG agrees and has changed recommendation 1.3.7 to 'Observe the inhaler technique…'. The GDG also agrees that inhaler technique should be checked 'when there is deterioration in asthma control' and has added this point to the recommendation.

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				demonstrate that they can use it. If they cannot use it properly, they need to be taught by a healthcare professional who is competent to teach inhaler technique. If they cannot grasp how to use that inhaler, it may be necessary to switch them to an alternative inhaler. Your three categories below are therefore over-simplistic. • *At every annual review* This does not go far enough. Healthcare professionals should be asking patients to demonstrate their technique at every encounter in any setting, including when picking up scrips from pharmacists. • *After every asthma attack* We agree that after any loss of control of asthma, including an attack, a healthcare professional should undertake a review with the patient to review their treatment, check their inhaler technique, and support the patient in knowing the signs to watch for, which might indicate that control is deteriorating i.e. to support the patient in self management. This should be done in hospital before discharge, if the attack has been serious enough to require hospital care, and certainly in primary care for follow up after discharge.	

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				• *When the device is changed* This is missing the point that inhaler technique needs to be checked whenever there is loss of control in order to determine whether the cause may be poor technique. So the situation should read '*When there is loss of asthma control*' not '*When the device is changed'*. If correcting poor technique enables the patient to get more benefit from the inhaler, it may not need to be changed.	
National Inhaler Group	Appendices NICE	664 256	N1.1.4.	We are very pleased to see that you have identified a research question on inhaler technique. Your analysis of the paucity of evidence, and the importance of understanding the most effective and cost effective approaches to teaching inhaler technique are excellent. We would welcome working with NICE on this important issue as it is central to our workstream on education and training of healthcare professionals on inhaler technique.	Thank you for your comment. NICE future research recommendations are reviewed by NIHR NETSCC and assessed for suitability for funding.
National Paediatric Respiratory and Allergy Nurses Group	Full	General	General	Very few children (even those within many centres who have a difficult/severe asthma service) will have a FEV1 <70% predicted.	Thank you for your comment. A footnote on the diagnostic cut-off values for children has also been added to the recommendations on spirometry and BDR.

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(NPRANG)					
National Paediatric Respiratory and Allergy Nurses Group (NPRANG)	full	General	General	Many centres do not use FeNO, some only in the severe asthma patient group. This is because there is still very much debate in the use of FeNO, caused by the lack validation in the use of FeNo in children. We would advocate that this is not used as a diagnostic tool. There will be many practical implications if introducing to primary care, let alone the cost of purchasing and maintenance of the equipment but training issues.	Thank you for your comment. The primary aim of this clinical guideline was to produce the most clinically and cost effective way to diagnose asthma accurately. The GDG acknowledge that the introduction of FeNO in primary care will require initial investment and training. However, the health gains and improvements in patient outcomes have been shown to be clinically effective as well as cost effective for the NHS; please see the health economic analysis in appendix M. The NICE Implementation team will produce support materials to facilitate uptake of the guideline into clinical practice.
National Paediatric Respiratory and Allergy Nurses Group (NPRANG)	Full	General	General	There is no mention of the response to medication and the importance of a structured asthma review when diagnosis is made. Many of us use a "trial of therapy" as a diagnosis of asthma in children.	Thank you for your comment. Trials of treatment are certainly used traditionally, but there is little formal evidence to support their use. We note that BTS/SIGN also found no good trial evidence and that the use of a trial of treatment is graded as a Good Practice Point for children and a Grade C recommendation for adults within that Guideline. A counter view is that they can lead to misdiagnosis when a natural improvement in symptoms coincides with, and is spuriously attributed to, introduction of asthma therapy. The proposed diagnostic sequence allows their use in cases of genuine doubt (see

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					algorithms B1 & C) but encourages the use of more objective tests beforehand. The guideline covers the importance of a structured asthma review, but there was no evidence that a review should be performed as soon as the diagnosis is made.
National Paediatric Respiratory and Allergy Nurses Group (NPRANG)	Full	General	General	There is no mention of the categorisation of diagnosing young children with asthma as advised by the BTS/SIGN guidelines. This is crucial in young children in whom objective measurement is not always possible or conclusive.	Thank you for your comment. Is this a reference to the idea of assessing probability of asthma on the basis of history and examination? The GDG did not find any evidence to guide subsequent investigations and management based on this initial categorisation.
National Paediatric Respiratory and Allergy Nurses Group (NPRANG)	Full	General	General	In our experience many primary care centres refrain from using spirometry in children under 16 . This is due to many health professionals in primary care lacking the expertise/ confidence or support they require to run these services.	Thank you for your comment. The GDG acknowledges that the implementation of some objective tests in primary care will require initial investment and training.
National Paediatric Respiratory and Allergy Nurses	Full	General	General	Bronchodilator reversibility/variability caused great confusion within the committee – as this guideline appears to contradict itself throughout the document. It also contradicts BTS guidance and ARTP guidance.	Thank you for your comment. The only difference from the BTS/SIGN guideline is the cut-off threshold specified for BDR. You do not specify, and we do not see, how we have contradicted ourselves within the guidance.

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Group (NPRANG)					
National Paediatric Respiratory and Allergy Nurses Group (NPRANG)	Full	General	General	Peak flow monitoring caused a great deal of debate as although we fully recognise that many GP areas will be using it as a tool to measure asthma management. It needs to be recognised that there is a debatable technique in the 5 – 9 year old age group and because of this many centres do not use peak flow but will prefer to rely on a structured asthma review and maybe a trial of medication.	Thank you for your comment. The GDG recognises that PEF measurement may be less rigorous and less technically competent in some users than in others. However, as you note it is strongly supported by primary care. We do not agree that trials of treatment should be given on the basis of symptoms alone. Trials of treatment are certainly used traditionally, but there is little formal evidence to support their use. We note that BTS/SIGN also found no good trial evidence and that the use of a trial of treatment is graded as a Good Practice Point for children and a Grade C recommendation for adults within that Guideline. A contra view is that they can lead to misdiagnosis when a natural improvement in symptoms coincides with, and is spuriously attributed to, introduction of asthma therapy. The proposed diagnostic sequence allows their use in cases of genuine doubt (see algorithms B1 & C) but encourages the use of more objective tests beforehand.
National Paediatric Respiratory	Full	General	General	We are concerned that this guideline appears very adult orientated – ie asking about work etc That we can understand the recommendation of spirometry to	Thank you for your comment. Recommendation 1.1.7 is specifically for the purpose of identifying occupational asthma, not to provide an emphasis on

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and Allergy Nurses Group (NPRANG)				establish diagnosis of COPD . However a stronger paediatric "flavour" would be recommended – so as to support our colleagues in primary care.	adults in the whole guideline. You will note that it is applicable to people of all ages in employment and does not exclude children who may also have occupational asthma (e.g. a young person 16 years old working in a bakery). The recommendation to measure spirometry is to aid asthma diagnosis, although we agree it is also important in COPD. You will see that there are specific recommendations for children of all ages throughout the guideline.
Neonatal and Paediatric Pharmacists Group (NPPG)	NICE	21-2	1.3.7	We agree that inhaler technique should be monitored after every asthma attack, when the device is changed, and at every annual review.	Thank you for your comment.
Neonatal and Paediatric Pharmacists Group (NPPG)	Full	256	6-9	We are pleased to see the list of healthcare professionals who need to keep their understanding up-to-date in order to provide education and support. However, we would like to see both community and hospital pharmacists and pharmacy technicians included in this list.	Thank you for your comment. We have made this change.

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Neonatal and Paediatric Pharmacists Group (NPPG)	Full	261	28	We are pleased to see the research recommendation regarding the current and optimal frequency and best method of checking inhaler technique to improve clinical outcomes for people with asthma.	Thank you for your comment.
Neonatal and Paediatric Pharmacists Group (NPPG)	NICE	26	3.4	As above.	Thank you for your comment.
NHS England	Full			As the introduction to the guideline makes clear, asthma may be a very difficult diagnosis to make because there is no single objective diagnostic test or indeed an agreed definition of the condition. We welcome the attempt to make an accurate diagnosis of a common condition which by common consent is poorly done (i.e 30% currently don't have the condition and others are missed). Patients deserve accurate characterisation.	Thank you for your comment.
NHS England	Full	General	General	This guideline is ambitious and technical in approach. The bulk of asthma diagnosis and care is delivered in the primary care setting and therefore the guideline should be acceptable and deliverable largely through general practice. However, it is not overly clear in the guideline at what stage referral to specialist	Thank you for your comment. Recommendations 1.2.5 for adults and 1.2.10 for children 5-16 provide the circumstances for referral for specialist assessment. The movement to specialist care has been

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				departments is deemed necessary.	thoroughly discussed in the economic model write up in appendix M. The movement from primary to secondary care occurs when the individual is in need of a challenge test. All other tests assessed in the pathway are assumed to be performed in primary care.
NHS England	Full	General	General	Implementation will be costly. The overall impression is that these ambitious guidelines may be implementable in a specialist environment but not easily in the present primary care structure. The vision of commissioned services in the Five Year Forward View may make it easier. For the time being, the impact of the recommendations would be offset if they were used only when there is diagnostic uncertainty in the mind of an experienced clinician.	Thank you for your comment. We agree that implementation is likely to take some time.
NHS England	Full	General	General	The guideline points out that the diagnosis of asthma is principally made by an experienced clinician with the assistance of some objective measurements of airflow obstruction, hyperresponsiveness or airway inflammation. Asthma is a highly variable condition and therefore it is possible to have asthma with none of these features currently present and the experience of the clinician is therefore vital to the security of the diagnosis.	Thank you for your comment. We agree, but it is hard to define experience in this context and therefore hard to capture this in a recommendation.
NHS England	Full	General	General	The guideline diagnostic algorithm for adults suspected of having asthma includes objective tests of spirometry,	Thank you for your comment. Currently, with the exception of bronchial challenge test with histamine

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				bronchodilator reversibility, exhaled nitric oxide and finally bronchial challenge testing. It is not entirely clear how much of this is expected to be performed in primary care or outside specialist units. Most hospital respiratory departments should be able to provide such a service.	or methacholine, all recommended objective tests could be performed in primary care (and in the case of PEFv monitoring in the community). The GDG acknowledge that availability will vary at present but the guideline will be a vehicle to drive the change that is needed in clinical practice in this regard.
NHS England	Full	General	General	If it is intended that the bulk of diagnostic activity is retained in primary care, as it is now, then there will have to be significant investment in training and equipment to meet the expectation. The cost estimate of spirometry, bronchodilator reversibility and FENO was estimated as £43 in a previous NICE document (there may be 5.4 million people with asthma in the UK). As a consequence, it is likely that many practices will simply refer to hospital specialists earlier than they would have done previously.	Thank you for your comment. The primary aim of this clinical guideline was to produce the most clinically and cost effective way to diagnose asthma accurately. The GDG acknowledges that the implementation of some objective tests in primary care will require initial investment and training. However, the health gains and improvements in patient outcomes have been shown to be clinically effective as well as cost effective for the NHS; please see the health economic analysis in appendix M.
NHS England	Full	General	General	The training requirement will also be substantial. Whilst many practices may have access to spirometry, the ability to interpret the tests is not widespread. The competency framework to deliver quality assured diagnostic spirometry developed as part of the DH Respiratory Programme Board legacy has not been published. The training needs for FENO are unknown and few practices have existing facilities. It is unlikely that bronchial hyper responsiveness studies could be	Thank you for your comment. Again, we agree. The implementation of some of these tests in primary care will require initial investment and training.

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				conducted outside a lung function laboratory.	
NHS England	Full	General	General	Diagnostic spirometry for children has even less availability than for adults and additional training over and above that required for adults would be needed. It is welcome that serial peak flow recording is an option here. In secondary care, the lung function services for children are less well developed and since the incidence of asthma is higher in children these services may be rapidly overwhelmed. However the use of diagnostic spirometry in children, who are of an age to perform the tests, is haphazard in its application and ideal of this documented should be recommended for secondary care and above.	Thank you for your comment. We agree that these problems are greater still in children, but the paediatrician members of the GDG were adamant that spirometry can be useful in diagnosis and that an attempt to measure this in older children should be made.
NHS England	Full	General	General	The monitoring of asthma care section is sound and recommends assessment of asthma control, objective airway function and importantly, inhaler technique at annual review or after change of treatment or exacerbation.	Thank you for your comment.
NHS England	Full	General	General	The lack of clarity on what stage referral to specialist departments is deemed necessary impacts upon the economic analysis that has been carried out. The overall impression is that these ambitious guidelines may be implementable in a specialist environment but not as easily in the present primary care structure. The balance to which delivery takes place in a primary care rather than a specialist environment is a significant	Thank you for your comment. The movement to specialist care has been thoroughly discussed in the economic model write up in appendix M. The movement from primary to secondary care occurs when the individual is in need of a challenge test. All other tests assessed in the pathway are assumed to be performed in primary care.

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				factor in economic analysis but it is unclear what assumptions have been made in this regard. The vision of future models of care in the Five Year Forward View may support implementation and should also be taken into account in the economic analysis. An alternative for use within current service models that could also be analysed is for the recommended approaches to only be used where there is diagnostic uncertainty in the mind of an experienced clinician.'	
NHS England	Full	1.1.10		Using a fixed FEV1/VC ratio may over-diagnose airway obstruction in older patients. Lower limit of normal of the ratio may be safer. Bronchodilator reversibility of this degree is not diagnostic of asthma alone and may be present in COPD or overlap syndrome.	Thank you for your comment. We agree that the fixed ratio may be misleading the nearer an individual is to the age extremes. The GDG debated recommending on the basis of LLN, but were aware that in primary care existing spirometers may not give these data. They decided to be pragmatic on this issue, and to recommend 70% as a cut-off. This will not misclassify many patients, and furthermore spirometry is not the only test recommended. The recommended level of bronchodilator reversibility was the best in the papers available to the GDG.
NHS England	Full	1.1.21		Exercise induced bronchoconstriction may be the only manifestation of asthma in some patients. This is particularly true in athletes where a supervised exercise	Thank you for your comment. Please see chapter 20 for the review of evidence for exercise challenge tests. The GDG did not consider the diagnostic

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				test or eucapnic hyperventilation examination may be required for confirmation.	accuracy was sufficient to recommend exercise challenge tests in adults over and above the diagnostic accuracy of the objective tests in the diagnostic pathway. The GDG considered there may be some utility in exercise challenge tests in children and hence recommended a future research recommendation to investigate the utility of exercise challenge tests as part of a diagnostic algorithm for children.
NHS England	Full	General		There is no mention of induced sputum eosinophilia for diagnosis or monitoring.	Thank you for your comment. Sputum eosinophil testing is outside scope. Stakeholder responses at scoping suggested that it was not routinely available in the vast majority of centres.
NHS Stockport CCG	NICE	4	9	We can't understand why you are recommending FeNo, at additional cost and staff resource for the NHS when you state 'Testing for airway inflammation is increasingly used as a diagnostic strategy in clinical practice. This includes measuring fractional exhaled nitric oxide (FeNO). However, there is **some uncertainty about both the sensitivity and specificity of FeNO, particularly in regard to whether it can distinguish general atopy from asthma'.** Costing impact in unclear around equipment, training of staff, lack of experience in primary care. Although it appears	Thank you for your comment. The sentence you quote is from the introduction to the guideline, which simply sets the scene for what follows. In this particular instance we are stating why it was thought appropriate to consider FeNO (if everyone was already using it and convinced of its worth, there would be less reason to look at it in such depth). The chapters on FeNO explain why the test is recommended.

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				relatively cheap and a quick test to perform we wish you to note concerns over its evidence	
NHS Stockport CCG	NICE	8	10	It is suggested all adults and children >5years would have spirometry and those with an obstructive pattern BDR in addition. In the supporting guidance and evidence document it suggests time allocated for this is 10-15mins. At many of our practices, the practice nurse is allocated 30mins for diagnostic spirometry - this time is used for explain to the patient, performing the test, interpretation, documentation and cleaning of the machine, We think NICE have significantly under-estimated the time taken to perform this diagnostic test. The impact on primary care would be mainly in practice nurse time & access to testing as not all practices have it available on site. We are uncertain if there is capacity to take on this huge patient group for spirometry in our primary care system, without significant resourcing.Have NICE considered these resource impacts?	Thank you for your comment. The time taken to perform a spirometry was based on expert consensus. In the adult model if the time used to conduct the test is doubled to 30 minutes then the use of spirometry remains cost-effective. Although there may be higher resource constraints that are incurred up-front when the disease is diagnosed, without these objective tests asthma may be mis-diagnosed and the costs to the NHS will be much higher in the long run. Resources may be freed up in primary care in the future if the number of mis-diagnoses were to decrease.
NHS Stockport	NICE	8	10	Our concern with spirometry in children is their ability to	Thank you for your comment. The GDG acknowledges that there is a paucity of diagnostic

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CCG				perform the test sufficiently to get meaningful data to interpret and the evidence presented is weak.	test accuracy data in children and hence made a high priority research recommendation to elucidate the best diagnostic pathway. The GDG has amended the recommendations for FeNO and BDR from 'offer' to 'consider' in children to reflect the evidence base. Furthermore, the GDG has added a caveat to the diagnostic algorithm for children to account for those children who are unable to perform objective tests from age 5 onwards that the principles in recommendation 1.2.1 should be followed until the child is old enough to perform objective tests adequately.
NHS Stockport CCG	NICE	16	2	We have no concerns over the use of PEFR variability monitoring as a rule IN test although does prolong the time taken to diagnosis and requires the patient to comply and return with results which can be a challenge	Thank you for your comment.
NHS Stockport CCG	NICE	17	15	Direct Bronchial challenge testing would only be for those >16years with significant diagnostic uncertainty and would involve secondary care referral for this to be performed increasing commissioning costs. The guideline states that bronchial hyperactivity varies over time therefore this test cannot rule asthma out, would this mean they would need testing on a number of occasion? This would have implications for	Thank you for your comment. The algorithm does not imply multiple challenge tests are needed. Whilst it is true that level of reactivity can vary this will only be a practical issue for those (a minority) whose results are close to the diagnostic threshold.

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				commissioning.	
NORTH EAST LONDON FOUNDATION TRUST	Full	General		Are any elements of this guidance likely to go into QOF once finalised?	Thank you for your comment. The GDG does not have direct input into QOF. We would expect QOF to take note of Guideline recommendations.
NORTH EAST LONDON FOUNDATION TRUST	NICE		8	Will there be support for CCG's to implement FENO testing? SIGN says it is available in secondary care.	Thank you for your comment. Use of FeNO is demonstrated to be cost-effective within the guideline, but the GDG does not have a role in determining funding and cannot answer your question.
NORTH EAST LONDON FOUNDATION TRUST	NICE		9	1) Is there a recommendation on how this is done? Is the in-check device appropriate to use? Especially if the patient forgets to bring their own device in. 2) will NICE provide a structured annual review tool to be used which is linked to in document?	We are not clear what this comment relates to and cannot provide an answer based on the information provided.
North West Severe Asthma Network	Full	General		There are many aspects of this work to be applauded: it is good to see that NICE is convinced that diagnosing asthma accurately (through the use of additional tests) is important, and has rightly drawn attention to very important aspects such as assessment for occupational asthma, using validated questionnaires, monitoring adherence, etc. Our concerns and suggestions are outlined below	Thank you for your comment.

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North West Severe Asthma Network	Full	General		The **rationale** behind this work is not clearly explained: • In the introduction (P13 l16) it is stated that 30% of patients diagnosed do not in fact have clear evidence of asthma. The only source of this critical figure appears to be the Aaron paper mentioned on P164 line 6. There are a number of reasons to suggest this is an overestimate of unknown, but potentially enormous size: 1. Aaron et al looked for confirmation of "currently-active" asthma in people who had a previous diagnosis of asthma (15-20 years earlier on average). This is not at all the same as looking for asthma in symptomatic patients at the point of a new diagnosis being sought. We all know that asthma is a variable disease and there is no way of knowing how many of these 30% did indeed have active asthma at the time of their original diagnosis 2. Further, two thirds of these "asthmatics" had not needed to take treatment or seek health care advice for > six months prior to their assessment. Again therefore these are not the same population in whom this guideline would	Thank you for your comment. For the statement "almost a third (30%) of adults do not have clear evidence of asthma" the guideline development group is aware of other evidence (5 references are given below) that suggest a large proportion of people treated for asthma at a single point in time do not have objective supportive evidence, or had normal objective tests. This is not to say that they were all misdiagnosed. The other possibilities are that their treatment has been so effective as to make all objective findings normal (in which case stepped-down treatment should be considered), or that spontaneous changes in an intrinsically variable condition have meant that, at that moment in time, all objective findings were normal. Without incidence studies with tests done at the time of presentation and diagnosis, the true figure is unknown. The GDG regrets that, in retrospect, undue emphasis was placed on over-diagnosis in our write-up. The aim of the Guideline is to improve overall accuracy of diagnosis. 1. Starren ES, Roberts NJ, Tahir M, O'Byrne L, Haffenden R, Patel IS, Partridge MR. A centralised

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				be used. 3. Only ~500 people were sampled, and there is an enormous risk of selection bias with those sceptical about their diagnosis surely far more likely to respond. 4. The diagnosis in this paper was secured on a physiological basis (BDR and/or BHR), whereas the NICE algorithm requires a high FENO as well. The exact phenotypes identified in each therefore are not exactly the same (although will clearly overlap) • As this 30% figure appears to be so critical to the rationale we feel the source data should have undergone a thorough critical review. Whilst we hope that this happened, there is no evidence of this in the document and the number is quoted without question throughout. • In light of the above the wording of the press release that highlighted this figure was regrettable. It will no doubt have caused significant anxiety in a lot of people with asthma, and may indeed have had a negative impact on adherence	respiratory diagnostic service for primary care: a 4-year audit<http://www.ncbi.nlm.nih.gov/pubmed/22430040>. Prim Care Respir J 2012; 21(2): 180-186 2. Linden Smith J, Morrison D, Deveau C, Hernandez P. Overdiagnosis of asthma in the community<http://www.ncbi.nlm.nih.gov/pubmed/15045041>. Can Respir J 2004;11(2):111-16. 3. Aaron SD, Vandemheen KL, Boulet LP, et al. Overdiagnosis of asthma in obese and nonobese adults<http://www.ncbi.nlm.nih.gov/pubmed/19015563>. CMAJ 2008;179(11):1121-31. 4. Marklund B, Tunsater A, Bengtsson C. How often is the diagnosis bronchial asthma correct<http://fampra.oxfordjournals.org/content/16/2/112>? Fam Pract 1999;16(2):112-16. 5. Shaw D, Green R, Berry M, Mellor S, Hargadon B, Shelley M, McKenna S, Thomas M, Pavord I. A cross-sectional study of patterns of airway dysfunction, symptoms and morbidity in primary care asthma http://www.ncbi.nlm.nih.gov/pubmed/22786814 Prim Care Respir J. 2012 Sep;21(3):283-7. doi: 10.4104/pcrj.2012.00057 Regarding the NICE press release, this issue has

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					been referred to the NICE press office for consideration.
North West Severe Asthma Network	Full	General		What is the evidence that the current British Thoracic Society guidelines are inadequate for accurate diagnosis? It is our collective opinion as a group of physicians with a strong interest in asthma that the problem is not that they are not suitable, but that they are not being followed. The fact that the proposed NICE guideline makes the diagnostic pathway even more complicated, time- and labour-intensive and more expensive we feel would make it even LESS likely to be followed. It therefore seems difficult to justify widespread change without evidence to support it. In addition we cannot have two conflicting sets of diagnostic (and management) guidelines from two UK bodies (NICE and the BTS). We would propose that the two bodies work together on the next draft of this document as a joint project	Thank you for your comment. The GDG does not feel that the recommendations on diagnosis in the NICE guideline are vastly different from that of BTS/SIGN. The NICE guideline provides more detail of when to perform certain objective tests. We agree that misdiagnosis would already be less common if the BTS/SIGN guidelines were followed more closely.
North West Severe Asthma Network	Algorithms	1-3		As a continuation from point 3 above, these algorithms are simply too complicated. It takes a minimum of three tests (after the history and examination) to get to a diagnosis – spirometry, reversibility, FENO – requiring a minimum of two visits. The current availability and of the first two in primary care is highly variable, and the latter virtually non-existent. A large investment in	Thank you for your comment. The primary aim of this clinical guideline was to produce the most clinically and cost effective way to diagnose asthma accurately. The GDG acknowledge that the implementation of some objective tests in primary care will require initial investment and training. However, the health gains and improvements in

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				training and equipment would therefore be required, without evidence of likely benefit to patients	patient outcomes have been shown to be clinically effective as well as cost effective for the NHS; please see the health economic analysis in appendix M. Multiple tests are necessary within this because no individual tests has sufficiently high specificity and sensitivity. Your comment also implies that in current practice asthma diagnosis can be made more swiftly. The currently used diagnostic method which is far less prominent in the NICE pathway is a trial of treatment, but this takes at least two visits.
North West Severe Asthma Network	Full	153	"other considerations"	"A FeNO test could easily be performed after a spirometry or BDR test at a low marginal cost" • This is incorrect: spirometry and BDR testing can lead to erroneous FENO readings (spirometry decreases it, and bronchodilation increases it - Silkoff et al. *Am J Respir Crit Care Med.* 1999;159:940-4). Hence a minimum of two visits are required before diagnosis	Thank you for your comment. The papers suggesting an effect of salbutamol or spirometry on FENO tend to be older papers and do not necessarily use modern FENO equipment. The effect is not present in all papers and when present is typically small.
North West Severe Asthma Network	Full	29	3	We have concerns that the subtleties of grading the strength of the evidence by the GRADE leads to confusion and difficulties in interpretation for practitioners.	Thank you for your comment. The NICE Asthma Diagnosis and Monitoring guideline has been developed in line with the processes outlined in the NICE Guidelines manual 2012. The methods used to assess literature in this review are according to

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					the robust methods and standards set by NICE (for further information please refer to the methods section of this guideline and the NICE manual - http://www.nice.org.uk/article/PMG6/chapter/1%20Introduction). Please also refer to the NICE website (http://www.nice.org.uk/article/pmg20/chapter/reviewing-research-evidence) which outlines the processes behind GRADE. The GRADE approach has been used in the development of NICE clinical guidelines since 2009. GRADE is a system developed by an international working group for rating the quality of evidence in systematic reviews and guidelines; it can also be used to grade the strength of recommendations in guidelines. NICE adopts the GRADE approach because a systematic approach to grading the strength of recommendations can minimise bias and aid interpretation. The key difference from other assessment systems is that GRADE rates the quality of evidence for a particular outcome across studies and does not rate the quality of individual studies. For more details about GRADE, see the Journal of Clinical Epidemiology series, appendix K and the GRADE working group website.

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					The GDG used their clinical and personal expertise and experience to appropriately interpret the clinical evidence presented, taking into account the quality. The evidence presented and the GDG interpretation of that evidence is discussed in LETR section.
North West Severe Asthma Network	Full	General		If these guidelines were implemented as they stand, they would necessitate a simultaneous implementation of new treatment guidelines with deletion of the current BTS Step 1; if the diagnostic process clearly demonstrates an active inflammatory component, then surely treatment must start with inhaled corticosteroids (which, incidentally, many of us in the NWSAN are supportive of)	Thank you for your comment. NICE is currently scoping for a new asthma management guideline and we anticipate that this point will be addressed within that work.
North West Severe Asthma Network	Full	169 table 18.6		We feel the health economic evaluation may not have taken all considerations into account, e.g.: • The diagnostic pathway will take an extra visit as noted in point 5 above as FENO cannot be performed after spirometry or BDR • We assume this model relies on every primary and secondary care practice in the UK investing in the necessary tests ("economy of scale"). If this feasible and reasonable? • The costs of alternative strategies e.g. incorporating blood eosinophil assessment, may not have taken into account the fact that for	Thank you for your comment. Your first and last bullet points have been answered in response to earlier comments. Blood eosinophil measurement was considered in the guideline and is not included in the diagnostic algorithms as explained in chapter 17 of the full guideline. Our assumptions about treatment of people with a diagnosis of asthma are based on current practice, and this applies to both those with a correct diagnosis and an incorrect diagnosis. If the treatment pathway changes, the assumed treatment would again change in each group. In summary, we

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				many patients a historic result may be available on file and hence a new test not required. • As noted in point 7 above the treatment guidance will have to change if this strategy is implemented, which will obviously have an impact on treatment costs • As noted in point 2 we do not feel the 30% figure of misdiagnosis can be justified by the evidence We therefore propose that the economic modelling should be fully set out and justified (and indeed as noted in point 10 below, redone when informed by new evidence)	do not think any of these points necessitate a complete re-working of the economic model. Your 2nd point is more relevant to implementation than to the economic model. The GDG acknowledge that FeNO testing in primary care is new and will require initial investment.
North West Severe Asthma Network	Appendices	22-23		Conflict of interest: Prof Mike Thomas • The impact of these guidelines, if implemented, on sales related to FENO will be dramatic – every GP and secondary care practice that wishes to diagnose asthma will have to buy a device and consumables. We note Prof Thomas' extensive conflicts of interest in this regard, and that quite rightly he withdrew from discussions surrounding FENO. We feel however that he should have been replaced for the whole consultation. o First (even though he withdrew from	Thank you for your comment. Professor Mike Thomas's conflict of interest was managed in concordance with the NICE declarations of interest policy. We disagree that there was insufficient expertise on the GDG to make appropriate judgements on the evidence. The remaining primary care members continued to make an excellent contribution to the discussions when Professor Thomas's views were not available.

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				FENO discussions) we feel it is not appropriate that a key member of the committee has spoken so frequently on the main manufacturer's behalf (Aerocrine), and indeed features fairly prominently on their website. His conflict of interest should be seen to not only impact directly the discussion of FENO but indirectly the discussion of all other aspects of the diagnostic pathway (as these would involve potential competitors to FENO, e.g. blood and sputum eosinophils) ○ Second, (and possibly more importantly) his withdrawal significantly impacted primary care representation on the panel – leaving one GP partner and one primary care nurse practitioner, with (as far as we can tell) very limited (perhaps no) experience of appraising research evidence. We therefore have reservations that the impact on primary care has been assessed properly. • On a related note it is regrettable that Aerocrine have chosen to use this draft guidance as a	We would also note that there are no 'key' members of the GDG; all GDG members have equal standing and no single GDG member's opinion takes precedence over another. The GDG has no input or control over Aerocrine's marketing strategy. However, this refers to the NICE DAP on FeNO, which is final published guidance, not the draft NICE clinical guideline.

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				marketing opportunity. The front page of their website now states "NICE recommends FENO...." Without any suggestion that in fact these are just draft guidelines	
North West Severe Asthma Network	Full	General		We do think the proposed novel diagnostic strategies are interesting and merit further investigation, but that there is not yet enough evidence to support their introduction. • We propose that they be investigated in pilot studies to evaluate their impact compared to current BTS guidelines • Informed by this a full economic evaluation and impact assessment should be undertaken • The next draft should be produced jointly with BTS / SIGN • One suggested option to consider for future implementation may involve the founding of local diagnostic hubs at the interface of primary and secondary care, with responsibility for all new diagnoses of asthma	Thank you for these suggestions. Your suggestion regarding diagnostic hubs certainly has merit, but again this is outside NICE's remit and would be a matter for local implementation.
Novartis Pharmaceuticals UK Ltd	NICE	4	Last paragraph on the page	We suggest greater clarity in the document confirming that this guideline is not intended for the diagnosis and monitoring of severe asthma patents. As stated in the developer's response in the stakeholder consultation comments document ''Severe and difficult to control	Thank you for your comment. Clarification has been added to the introduction that the guideline does not cover people with severe, difficult to control asthma.

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				asthma' is a clearly defined and separate sub group distinct from the wider asthma population and the investigations involved in the diagnosis and monitoring of this population are outside the scope of this guidance'. We suggest adding the following statement to the final paragraph, 'This guideline is not applicable for the diagnosis and monitoring of patients with severe asthma. Severe asthma patients should be referred and managed in tertiary care.'	
Novartis Pharmaceuticals UK Ltd	NICE	5	First statement	Prescribers may also use published NICE guidance, as well as the summary of product characteristics, to inform decisions made with individual patients.	Thank you for your comment. This is standard NICE text in the template.
Novartis Pharmaceuticals UK Ltd	NICE	14	General	Consider adding statement such as "Aspects of history e.g. haemoptysis, may warrant further investigation and possible referral"	Thank you for your comment. This is outside the scope of the guideline.
Novartis Pharmaceuticals UK Ltd	NICE	16	Allergy testing	Whilst we acknowledge that allergy tests should not be used as a basis for diagnosis, they are useful to consider in terms of long-term management and identification of trigger factors. We request additional text be added to 1.1.15 to ensure this is clear.	Thank you for your comment. The GDG has added a recommendation to reflect the importance of allergy testing to identify asthma triggers.
Novartis Pharmaceuticals UK	NICE	14	Section 1.1	We suggest greater clarity regarding which diagnostic tests should be conducted in primary care versus specialist settings. A quick reference table may be	Thank you for your comment. Currently, with the exception of bronchial challenge test with histamine or methacholine, all recommended objective tests

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Ltd				helpful to users.	could be performed in primary care (and in the case of PEFv monitoring in the community). The GDG acknowledge that availability will vary at present but the guideline will be a vehicle to drive the change that is needed in clinical practice in this regard. Due to variability of current service provision we do not feel it is possible to provide this level of detail in a clinical guideline.
Novartis Pharmaceuticals UK Ltd	NICE	18-21	Section 1.2	Consider adding statement such as "If diagnosis is inconclusive consider referral to specialist centre".	Thank you for your comment. Please see recommendations 1.2.5 for referral in adults and recommendation 1.2.10 in children 5-16. The conditions in these recommendations are those that the GDG considered would warrant specialist referral. All other conditions the GDG considered were appropriate to be dealt with in primary care. The GDG has added 'consider referral for specialist assessment' to recommendation 1.2.11 in children with suspected asthma.
Novartis Pharmaceuticals UK Ltd	NICE	21-22	Section 1.3	Where loss of control is identified, immediate action is required, including treatment changes and potentially referral. Referral for specialist review should be considered in the following situations: • If patients fail to improve despite good inhaler technique, good compliance and optimised therapy	Thank you. The issue of referral for specialist care was not prioritised by stakeholders, and we have not done the relevant evidence search for this guideline. Referral is a potential topic for the forthcoming Asthma Management guideline.

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				• For patients with a history of hospital admissions / hospital emergency department visits or out of hours care in the previous year • For patients using reliever inhalers excessively (>12 in previous 12 months) • If patients have required two or more courses of systemic steroids, orally or injected in the previous 12 months. **We query whether a statement such as "patients with uncontrolled asthma despite optimised management and adherence to therapy should be referred for specialist review".** Consider adding in a review of the Personal Asthma Action Plan during monitoring. Alongside inhaler technique, flu (and pneumococcal for those patients on maintenance systemic steroids) vaccination/s should also be monitored.	
Novartis Pharmaceuticals UK Ltd	NICE	21	Section 1.3.1	People with asthma should have a review at least annually and asthma control should be monitored at every review. Patients with uncontrolled asthma may require more frequent review or referral.	Thank you for your comment.
Novartis Pharmaceuticals UK Ltd	NICE	General	Section 1.2 & 1.3	Diagnosis and monitoring should be conducted by clinicians with appropriate experience and expertise and nurses who have completed accredited asthma training. All HCP's involved in the care of patients with asthma	Thank you for your comment. Service delivery for asthma care is outside the remit of this guideline.

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				should ensure that their training is regularly updated. This is currently not specified within the draft guideline.	
Novartis Pharmaceuticals UK Ltd	Full	14	11	We suggest greater clarity in the document confirming that this guideline is not intended for the diagnosis and monitoring of severe asthma patents. As stated in the developers response in the stakeholder consultation comments document ''Severe and difficult to control asthma' is a clearly defined and separate sub group distinct from the wider asthma population and the investigations involved in the diagnosis and monitoring of this population are outside the scope of this guidance'. We suggest adding the following statement to the final paragraph, 'This guideline is not applicable for the diagnosis and monitoring of patients with severe asthma. Severe asthma patients should be referred and managed in tertiary care.'	Thank you for your comment. Clarification has been added to the introduction that the guideline does not cover people with severe, difficult to control asthma.
Novartis Pharmaceuticals UK Ltd	Full	45	21-22	We query whether the necessary results of the fractional exhaled nitric oxide (FeNO) test should be specified, rather than simply that the test has been conducted?	Thank you for your comment. At this point in the diagnostic pathway a FeNO test would have been conducted but the next step is not conditionally dependent on the FeNO results and hence the cut-off values have not been specified in this recommendation bullet point.
Novartis Pharmaceuticals UK Ltd	Full	69	Other considerations	We consider the statement "treatment would be similar regardless of atopic status" to be misleading. Whilst primary care treatment may be similar regardless of atopic status, in atopic patients with poorly controlled	Thank you for your comment. We have changed the sentence to read "Initial treatment…".

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				asthma an additional treatment option is available (omalizumab).	
Orion Pharma UK Ltd	NICE Full	28-30 16	General 3	List of Guideline Development Group: It appears that there has been some under-representation of Primary Care in the Guideline Development Group. The Group is largely secondary care focussed and this could have an impact on the primary care focussed HCPs who are conducting asthma reviews and checks in the everyday setting. We appreciate that there is a, a wealth of knowledge in the Group; we would encourage the group to be expanded to consider the experiences of delivering care in the primary case setting. Having reviewed the document it would be hard to see how much of what is suggested could be easily implemented in Primary Care. This would be the main query of the whole guidance being reviewed.	Thank you for your comment. There are two GP members and a primary care nurse practitioner. The guideline needed to have input from those with expertise in asthma in children and adults, and groups work better if they are not too large. The composition reflects these considerations. Stakeholders were consulted on the GDG composition at the start of guideline development.
Orion Pharma UK Ltd	NICE	16	General	Using Peak Flow (PF) as a monitor of variability is a good test if it is used over the period of 2 to 4 weeks and the patient has a diary to record symptoms alongside of this. PF meters need to be calibrated and the patients trained appropriately with the PF device. Concerns are already present in general practice that PF meters are not	Thank you for your comment. The GDG are aware of the unreliability of PEFv monitoring; please see section 13.6 on page 111 'Trade off' section last two paragraphs, and hence its position in the diagnostic pathway. Guidance on PAAPs is outside scope.

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				calibrated and may offer patient's incorrect readings. It could be stressed that PF is for monitoring over a period of time, and it is not uncommon for HCPs to use PF meters in a routine consultation, but this does not measure truly how the patient is over a period of time, but simply on that day at that time. PF is often incorrectly used to diagnose and monitor asthma. It should be stressed exactly why PF is done and why it is important to provide patients with the correct information so that they can monitor their PF at home. PAAPs (Personal Asthma Action Plans), as stated, could help to support the use of PF, but only if the full detail is explained to the patient of how important this is.	
Orion Pharma UK Ltd	NICE	17	General	FeNO testing is not widely used in primary care and could potentially add in extra burden for patient and healthcare professional if the HCP doing the FeNO testing is not adequately trained in what it is they are doing with the FeNO test. We are interested to know how widespread FeNO testing in primary care? For example, how many surgeries and practices in the UK actually have a FeNO machine? Will the cost of the purchase of the machine also be factored in to any future cost of asthma diagnosis, alongside training costs?	Thank you for your comment. The primary aim of this clinical guideline was to produce the most clinically and cost effective way to diagnose asthma accurately. The GDG acknowledge that the implementation of FeNO testing in primary care will require initial investment and training. However, the health gains and improvements in patient outcomes have been shown to be clinically effective as well as cost effective for the NHS; please see the health economic analysis in appendix M. The NICE Implementation team will produce support materials to facilitate uptake of the guideline into clinical

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					practice.
Orion Pharma UK Ltd	Full	28	16	There does not appear to be any inclusion of 'real world studies', about how patients are managed in routine clinical practice? These are not necessarily patients in RTCs or even in Case control tests or retrospective studies.	Thank you for your comment. For the assessment of diagnostic accuracy, cross sectional studies are considered the gold standard design. The index test and the reference standard test are applied to the same population, and agreement between the two tests is assessed. RCTs are considered the gold standard evidence base for interventional studies and were used to assess the effectiveness of monitoring. Prognostic studies were not included in these reviews. The GDG acknowledged that prognostic studies can show the association between the monitored clinical feature and future risk. However, the GDG wished to evaluate the effectiveness of monitoring each clinical feature to guide treatment on patient outcomes in an RCT design.
Orion Pharma UK Ltd	Full	49	24	What is the current frequency to check inhaler technique…… An additional question should be added to question *what* HCPs are doing if inhaler technique is not correct . According to SIGN/BTS (October 2014) patients should be offered a different device. This would prevent patients moving to 'step 3 'too quickly.	Thank you for your comment. The question which you suggest was not specified during stakeholder consultation on the scope. We also do not believe that there would be any formal evidence around this – it is self-evident that if a person cannot use an inhaled device despite instruction from a trained health professional, that an alternative device should be tried. We note that the advice you quote from the BTS/SIGN guideline is a Good Practice Point i.e.

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					based on consensus rather than evidence. Moreover, our interpretation of the relevant section of that guideline is that the first thing to do if inhaler technique is incorrect is to re-offer instruction with that device rather than automatically changing devices as you suggest.
Orion Pharma UK Ltd	Full	200	General	Orion Pharma were still awaiting the economic model to be received at the time of returning the proforma. As it is there were no real life studies included in the results of the economic section that can be seen. These can often show the financial benefits to HCPs in real patients, such as those that they see. There is data from real world studies that review cost effectiveness. Price D, Thomas V et al . Switching patients from other inhaled corticosteroid devices to the Easyhaler®: Is a historical, matched-cohort study of real-life asthma patients. (Journal of Asthma and Allergy 2014; 7: 31-51)	Thank you for your comment. We believe your comment is more directed towards the management of asthma whereas the economic model focused on the cost-effectiveness of diagnostic tests.
Orion Pharma UK Ltd	Full	247	General	It should be highlighted that patients at Step 2 of the BTS/SIGN guidelines can also be treated with once daily inhaled corticosteroids as this can aid compliance as opposed to increasing the steroid or adding in further medication in the form of a combination product. Again	Thank you for your comment. A consideration of once daily inhaled corticosteroids would have to take other factors into account, particularly efficacy, and is beyond the scope of this particular guideline.

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				this should be viewed in line with giving the patients an inhaler that they can and will use.	
Orion Pharma UK Ltd	Full	257	General	Where is the differentiation between DPI and pMDI in reviewing the inhaler technique of patients? Although DPIs can be seen in the analysis of studies, albeit far less than pMDIs, there is not appear to be any differentiation in the write up between the two types of inhaler. HCPs (along with patients) need to know that there is more than just one type of inhaler in the UK. Before moving up the asthma steps of BTS management (e.g. Step 2 to Step 3) patients should be assessed and changed device before stepping up treatment by their HCP. See also point 10 below.	Thank you for your comment. The questions addressed in this section are generic, comparing the effectiveness of monitoring inhaler technique with feedback vs. no monitoring of inhaler technique; and comparison of the effectiveness of monitoring inhaler technique using different methods. We considered all papers which met these criteria whether they involved MDI or DPI.
Orion Pharma UK Ltd	Full	261-263	General	The cost of monitoring inhaler technique is negligible as this could be carried out as part of routine visits. The problem with this statement is that inhaler technique *should* be carried out on routine visits when patients come for their asthma reviews, in reality, this is probably not happening routinely in UK general practice. Also there appears to be a lack of evidence in the document supporting the notion that patients do find pMDIs difficult to use (e.g. http://www.thepcrj.org/journ/view_article.php?article_id=	Thank you for your comment. We do indeed recommend checking inhaler technique at routine review, as well as on other occasions (see recommendation 1.2.6). The comparison of different types of inhaler is outside the scope of this guideline.

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				1069 looking at how technique training does not improve the ability of most patients to use pressurised metered-dose inhalers (pMDIs)Levy, Hardwell et al 2013). This has been shown in several studies that patients find pMDI inhalers hard to use	
Orion Pharma UK Ltd	Full	263	General	The GDG was in agreement with the NICE Quality Standard for asthma that inhaler technique should be assessed after every attack, with every change of inhaler device and at every annual asthma review. We would recommend that HCPs be reminded that they should be routinely checking inhaler technique, changing devices where appropriate, and moving up the BTS steps only when necessary.	Thank you for your comment.
Primary Care Respiratory Society UK	Full			KEY POINTS FOR ATTENTION • We have major concerns over this draft guideline and do not believe that it should appear in its current form. There are major challenges for implementation which it is important for NICE to recognise and consider.	Thank you for your thoughtful and comprehensive comments. You make a number of important points; some of these are mentioned again in your chapter-specific comments, and our responses to those points are given below. We agree that it is desirable for asthma diagnosis to be made in primary care wherever possible. All the

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				• We have major concerns over the potential adverse effects of having two differing guidelines for asthma diagnosis and asthma care (NICE and BTS/SIGN). This has significant implications for the education and training of health professionals and hence on patient care and patient outcomes. • We would strongly encourage NICE to co-operate with BTS /SIGN to produce a single consistent set of national guidance for people with asthma and the health professionals who care for them, and to devote more effort to the implementation of the extensive range of existing sound guidance. • We think that consideration needs to be given to an alternative diagnostic algorithm based on repeated clinical assessments, peak flow monitoring and trials of initiating and discontinuing therapy, with referral to specialist services in cases of doubt or difficulty. This option does not seem to have been considered, and should have been.	tests we recommend should be achievable without referral to secondary care, with the exception of bronchial challenge which will be required in only a minority of cases. It is true that there is an implementation challenge. FeNO testing is new; there are well recognised problems with quality control of spirometry. However, the health gains and improvements in patient outcomes have been shown to be clinically effective as well as cost effective for the NHS; please see the health economic analysis in appendix M. The NICE Implementation team will produce support materials to facilitate uptake of the guideline into clinical practice. The GDG disagree that the diagnostic algorithm is prohibitively complex. Patients who present to their GP with mild symptoms of asthma can perform spirometry, BDR and FeNO tests during a follow-up appointment with the practice nurse to get a positive diagnosis of asthma. A small proportion of patients with diagnostic uncertainty will go through the longer route in the diagnostic pathway in order to obtain further objective testing evidence of asthma. Trials of treatment are certainly used traditionally,

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				Introductory Comments / An overview Making a diagnosis of asthma is not simple. It is not possible to rely on any single clinical feature or test result and patients seen when they are well may have no symptoms , no abnormal physical signs and no physiological abnormalities : what is required is careful integration of evidence from a wide variety of sources – the clinical history, examination , physiological tests of airways obstruction and other supporting tests and investigations where necessary- with the need for at least some of these assessments to be repeated over time and in response to treatment before a confident diagnosis can be made. **This integration of information about an individual over time is best done in primary care , where the great majority of asthma diagnoses are currently made.** There is undoubted need for improvement: problems still exist with delay in diagnosis, misdiagnosis and over diagnosis. Mike Silverman and Duncan Keeley described some of the reasons for overdiagnosis of asthma in children in a	but there is little formal evidence to support their use. We note that BTS/SIGN also found no good trial evidence and that the use of a trial of treatment is graded as a Good Practice Point for children and a Grade C recommendation for adults within that Guideline. A counter view is that they can lead to misdiagnosis when a natural improvement in symptoms coincides with, and is spuriously attributed to, introduction of asthma therapy. The proposed diagnostic sequence allows their use in cases of genuine doubt (see algorithms B1 & C) but encourages the use of more objective tests beforehand. The diagnostic endpoints do factor in reviewing the diagnosis of asthma based on response to treatment. In regards to your queries about the economic modelling, the costs of training are not usually included in the cost effectiveness analysis for NICE clinical guidelines. This is because the cost effectiveness model assesses the costs per patient and therefore training costs tend to marginalise to zero over time as training isn't conducted per patient. Training costs however are something that the NICE implementation team may consider. The

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				paper in Thorax in 1999. (1) Reference : Thorax 1999;**54**:625-628 doi:10.1136/thx.54.7.625 Review series Issues at the interface between primary and secondary care in the management of common respiratory disease • 2 Are we too ready to diagnose asthma in children? Duncan J Keeley[a] Michael Silverman[b] **The key uncertainty is this: will these problems best be addressed by changes in the whole approach to diagnosis , or by better education of health professionals in using and integrating the various sources if clinical and diagnostic information already available? At a time of major resource constraint in the NHS this is a very important question, since it may not be possible to do both.** **A significant omission from this guideline on diagnosis and monitoring is any systematic discussion of the role of trials of therapy. Trials of therapy are very widely used by health professionals in asthma diagnosis and are a mainstay of the discussion of diagnosis in the existing NICE approved BTS/SIGN guideline. It seems strange to omit any discussion of the place	capital costs are included in the economic model. The NICE implementation team will produce a costings tool which looks at budget impact on the NHS. With regards to the economic modelling being underpinned by the evidence on current practice diagnostic accuracy. In the 'current practice' arm two more assumptions also imposed were that asthma is always perfectly diagnosed (sensitivity = 100%) and the costs of doing so are zero. Even with these assumptions in place the strategy was not cost-effective. The reference cited is the best evidence we have for what level of diagnosis may be and this is supported by numerous other references. A sensitivity analysis was also conducted whereby the specificity of 'current practice' was increased by 10% and the recommended diagnostic algorithm remained cost-effective at a £20,000 per QALY threshold.

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				of trials of therapy in diagnosis without a clear statement of the reasoning behind this omission. NCGC has in other respects conducted a thorough and methodologically rigorous review of published evidence relating to the diagnosis and monitoring of asthma. But in many areas of relevance to the guideline it has identified a remarkable scarcity – or absence - of sound clinical evidence. Many of the cited studies were judged to have substantial problems with risk of bias, serious inconsistency or indirectness, with the result that many of the recommendations rest primarily on the expert opinion of the guideline development group. Importantly the guideline has striven to provide the best possible cost analysis of its recommendations. But these analyses are necessarily based in part on assumptions and estimates which are imprecise; these assumptions are made explicit in the document. **Capital costs of acquiring spirometry and FeNO equipment, and the costs of training staff in their use, do not seem to figure in the cost estimates. We are also interested to know whether the cost of additional referrals and the overall cost to practice of implementing this guidance have been factored in.**	

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				No distinction is made in the literature identified to distinguish data from different populations: diagnostic approaches in primary care, secondary and tertiary care will be very different. The individual diagnostic tests have varying degrees of evidence behind them. However, the way they are used in the real world and how they fit together has little evidence , so the algorithms NICE has created attempt to piece together the different evidence based diagnostic interventions with little consideration for the way patients are seen in routine clinical care. **The diagnostic algorithms recommended in the report represent a massive change in current practice**. They mandate quality assured spirometry (with reversibility testing where obstructive spirometry is identified) for a diagnosis of asthma in all cases other than children under 5, and FeNO testing in the majority – (the exception being for children under 16 with demonstrably reversible obstructive spirometry – features which are judged adequate to make a diagnosis without resort to FeNO testing). Bronchial challenge testing with methacholine (only available in secondary care and not always there) is accorded a	

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				significant role in cases of doubt in the conclusions from spirometry and FeNO testing. Peak Flow Monitoring – an inexpensive, easily available and widely used method of documenting objective evidence of variable airflow obstruction – is retained but only for further clarification in cases of doubt or difficulty having used the more expensive and less easily available diagnostic aids first. Assessing the response to trials of therapy - as advocated by the current NICE approved BTS/SIGN guidelline and widely used by practitioners in both primary and secondary care – has no clear and explicit place in the diagnostic algorithm suggested by the new guideline. **We believe it is essential that NICE considers the gulf between current practice and the proposed changes to diagnosis and monitoring, or it will simply not be implemented.** **While quality assured spirometry and FeNO testing are both capable of being provided in primary care there are currently major constraints in their availability**. Spirometry is widely but not universally available in primary care, but there are concerns over the quality of its performance and interpretation. The Department of Health is preparing to issue a policy document which, by requiring ARTP equivalent training and recertification for those performing and interpreting	

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				diagnostic spirometry in primary care, may substantially reduce its availability pending significant investment in training for primary care personnel. Equipment for measuring FeNO is expensive and currently very few primary care practices have this equipment. The capital cost of acquiring the equipment appears to be omitted in the costings for FeNO used in the economic analyses. Thus, **under current circumstances, the guideline recommendations are likely to involve a substantial number of referrals to secondary care when a diagnosis of asthma is being considered, and substantial investment in both equipment and training will be required to change this** : currently also , given the adverse financial climate in which the NHS and primary care is operating, such investment would currently need to be at a direct cost to primary care practices whose incomes are falling. Practices are also under significant pressure from commissioners to reduce their rate of referral to specialist services. Given these challenges to implementation, the implications of the guideline recommendations and the soundness of the logic by which they are inferred from the (often surprisingly sparse) evidence base needs very careful consideration.	

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				It is not immediately obvious why an alternative strategy was not considered , namely that of using (repeated) clinical history and examination supported by peak flow monitoring and response to trials of therapy, with the reservation of spirometry, FeNO testing and if necessary bronchial challenge testing in cases of doubt or difficulty in diagnosis. We would question whether the same quality of evidence is available for the algorithms as for the individual diagnostic interventions. One hazard of an approach based primarily on published evidence is that of an undue influence on the conclusions by the number of studies available; there were 17 published studies of using FeNO in diagnosis but, for example no studies using PEFR charting to assess bronchodilator reversibility, and no studies of spirometry reversibility testing in children. New technologies have often been better evaluated than older and simpler diagnostic techniques. The principle health economic argument in favour of rendering the diagnostic process substantially more complex and expensive, and substantially more dependent on referrals to secondary care services , rests on the assumption – supported by reference to a	

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				single Canadian study in adults conducted in 2005-7 – that there is substantial overdiagnosis and unnecessary treatment of asthma. It is therefore inferred that savings in reduced treatment costs would offset the cost of a more complex diagnostic process. The cited study was based on a telephone survey for recruitment, and its authors acknowledged that volunteer bias may have led to an overestimate of the misdiagnosis rate. There is some doubt that this study can be considered relevant to the UK situation. *Reference : CMAJ* November 18, 2008 vol. 179 no. 11 doi: 10.1503/cmaj.081332 Overdiagnosis of asthma in obese and nonobese adults Shawn D. Aaron MD et al It is important also to mention the very significant changes proposed in the process of conducting regular reviews for people with asthma in primary care. Introducing a requirement for the use of the Asthma Control Test questionnaire, and of spirometry or " assessment of peak flow variability" as routine components of asthma reviews – whatever their merits – constitutes a substantial addition to workload in primary care at a time when primary care services are under major strain meeting other existing and new	

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				commitments. **There is a significant risk that the diagnostic algorithm proposed in the new guideline may cause more problems than it solves, by mandating a greater reliance on more costly investigations and on referrals to often hard pressed secondary care services with potential delays for other patients who really do need to be seen in secondary care. Better education in asthma diagnosis of doctors and nurses in primary and secondary care is vital, whether or not the new diagnostic approach outlined in the guideline is adopted. It is far from clear that the resources for this are available: there is already a widely acknowledged problem in driving the implementation of existing guidance and standards issued by NICE and others for improving asthma care.** **NICE needs to consider very carefully the implications of this guideline for the prioritisation of resource use in a climate of unprecedented financial difficulty for the NHS .** **The guideline seems more appropriate for use in secondary care than in primary care , and one**	

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				possibility would be to reframe it as a secondary care guideline , with a specific remit to improve the strength of the evidence base for asthma diagnosis. **In that setting it might be worth considering the possibility of recommending a process of piloting the use of the diagnostic algorithm recommended and assessing its effectiveness and the logistics of implementation before proposing its universal adoption.** PCRS-UK conducted a survey of its members to gather views on the proposed guideline. There were 91 responses – the highest ever for a piece of policy in development. The report is attached.	
Primary Care Respiratory Society UK	Full	1,2,3		The account of the methodological approach (Chapters 1 , 2 and 3) is a model of clarity	Thank you for your comment.
Primary Care Respiratory Society UK	Full	4		**Guideline Summary and Key Priorities for Implementation (Chapter 4**) – see introductory comments above	Thank you for your comment.

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Primary Care Respiratory Society UK	Full	6-10		**History Taking Approaches (Chapters 6-10**) - rigorous analysis of the evidence and sensible clear conclusions . However a history of previous use of anti asthma treatments and response – or lack of it - to these would be included by all clinicians when assessing a patient for a possible asthma diagnosis. Why is this key feature in the history omitted here? In common with every other aid to diagnosis a history of apparent response to asthma treatments should be treated with caution, but that is not a reason for not asking. Occupational Asthma 10.6 p 84 – recommendations – consider including here a recommendation for peak flow charting with marking of times at and away from work when referring to secondary care : this is often requested and found useful by chest physicians. BTS /SIGN says … *PEF records from frequent readings taken at work and away from work are useful*	Thank you for your comment. The diagnosis recommendations are for people who are under investigation for suspected asthma, not a previous diagnosis of asthma. The question about benefit, or lack of benefit, from anti-asthma medication is part of the assessment of a trial of treatment (see later comment/response). We agree that a person presenting with symptoms may have tried medication in the past, and if so that this should be asked about. The guideline cannot cover every possible scenario. Detailed assessment of occupational asthma is not in the scope of this guideline.

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				when considering a diagnosis of occupational asthma (see section 12.3.1). A computer generated analysis of occupational records which provides an index of the work effect is available.[101]	
Primary Care Respiratory Society UK	Full	11		**Spirometry Chapter 11** The capital costs of acquiring a spirometer , and the training costs of ensuring that staff and clinicians are competent in performing and interpreting the tests are not included in the costings. This is a consistent feature of the costing approach used in the guideline, but does mean that significant costs relevant to implementing the strategy are omitted,. **The very sparse evidence base for using spirometry in asthma diagnosis in children is copied below**. This seems a slim evidence base for recommending a major change in practice ie the use of spirometry for diagnosing asthma in children age 5-16. The survey of our members	Thank you for your comment. The capital costs of spirometry have been considered. Training costs have been omitted under the assumption that they marginalise to zero per patient over time as training is not conducted per patient. Training costs however are something that the NICE implementation team may consider when clauclating the budget impact. The evidence base is indeed sparser in children generally, including that around spirometry. The GDG debated this at length but the paediatricians on the group felt that good readings can be obtained, particularly in older children, that the information is potentially valuable, and therefore that the measurement should be attempted. The GDG agrees that many people asthma will have normal spirometry and have provided a diagnostic algorithm which covers this situation.

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				highlighted considerable concerns that children will struggle with spirometry, the mouthpieces are too large, the staff are not trained in its use in children, the predictive values in children are not validated. *Children 11* *No evidence was available for FEV1/FVC <70% in children 12* *No evidence was available for flow volume loop 13* *One study with 133 children showed that spirometry (FEV1 <80%) has a sensitivity of 52% and a 14 corresponding specificity of 72% for diagnosing asthma in people presenting with respiratory 15 signs and symptoms. (LOW QUALITY).* In adults the evidence base is somewhat better but still not overwhelming *In adults, there were five included studies; however, only one study reported the diagnostic accuracy of the FEV1/FVC ratio alone. The*	

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				evidence was of moderate quality. . Our members have highlighted that many people asthma will have normal spirometry.	
Primary Care Respiratory Society UK	Full	12		**Bronchodilator Reversibility Chapter 12** Again the evidence base for this (entirely logical , sensible and widely used) aid to asthma diagnosis is weak, with no relevant evidence at all in children . **Clinical 2** □ Two studies with 868 adults showed that bronchodilator reversibility (ΔFEV1%init ≥12% **and** 3 ΔFEV1[L] ≥0.2L) has a sensitivity range of 0.17 to 0.65 and a corresponding specificity range of 4 0.61 to 0.81 for diagnosing asthma in people presenting with respiratory signs and symptoms and 5 obstructive airways disease. (VERY LOW	Thank you for your comment. The GDG acknowledges that there is a paucity of diagnostic test accuracy data in children and hence made a high priority research recommendation to elucidate the best diagnostic pathway. The GDG has amended the recommendations for FeNO and BDR from 'offer' to 'consider' in children to reflect the evidence base. A footnote on the diagnostic cut-off values for children has also been added to the recommendations on spirometry and BDR. Furthermore, the GDG has added a caveat to the diagnostic algorithm for children to account for those children who are unable to perform objective tests from age 5 onwards that the principles in recommendation 1.2.1 should be followed until the child is old enough to perform objective tests adequately.

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				QUALITY) 6 □ Two studies with 269 adults showed that bronchodilator reversibility (ΔFEV1%init >15% **and** 7 ΔFEV1[L] >0.2L) has a sensitivity range of 0.69 to 0.69 and a corresponding specificity range of 8 0.55 to 0.71 for diagnosing asthma in people presenting with respiratory signs and symptoms and 9 obstructive airways disease. (LOW QUALITY) 10 □ No evidence was identified in children aged 5-16 years This illustrates nicely the way in which published clinical evidence may be very sparse for simple tests that are universally acknowledged to be of value in helping make a diagnosis of asthma (and are , sensibly , included in the algorithm by the GDG.	
Primary Care	Full	13		**Peak Flow Variability Chapter 13**	Thank you for your comment. In fact most people will get a measurement of PEF variability, because

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Respiratory Society UK				Here the evidence base is stronger : **Clinical 20** □ One study with 323 adults showed that PEF variability (mean amp%mean >5%) has a sensitivity of 21 0.56 and a corresponding specificity of 0.69 for diagnosing asthma in people presenting with 22 respiratory signs and symptoms. (MODERATE QUALITY) 23 □ One study with 323 adults showed that PEF variability (mean amp%mean >10%) has a sensitivity 24 of 0.14 and a corresponding specificity of 0.96 for diagnosing asthma in people presenting with 25 respiratory signs and symptoms. (MODERATE QUALITY) One study with 323 adults showed that PEF variability (mean amp%mean >15%) has a sensitivity 1 of 0.05and a corresponding specificity of 0.98 for diagnosing asthma in people presenting with 2 respiratory signs and symptoms.	most people will have non-obstructive spirometry and follow algorithm B2. The problem with PEF variability is that is not a sensitive test for asthma. We agree that it is specific, and a positive result is good evidence as a rule-in test, but the test will be negative in most people with suspected asthma. The GDG therefore felt that it was more efficient to measure spirometry first since those with airflow obstruction can have reversibility measurement plus FENO, and won't need the PEF variability testing.

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				(MODERATE QUALITY) 3 □ One study with 170 adults showed that PEF variability (amp%highest >15% on 4 days or more) has 4 a sensitivity of 0.20 and a corresponding specificity of 0.97 for diagnosing asthma in people 5 presenting with respiratory signs and symptoms. (HIGH QUALITY) 6 □ One study with 170 adults showed that PEF variability (amp%highest >20% on 3 days or more) has 7 a sensitivity of 0.12 and a corresponding specificity of 0.99 for diagnosing asthma in people 8 presenting with respiratory signs and symptoms. (HIGH QUALITY) 9 □ One study with 170 adults showed that PEF variability (mean amp%highest >10%) has a sensitivity 10 of 0.14 and a corresponding specificity of 0.97 for diagnosing asthma in people presenting with 11 respiratory signs and symptoms. (HIGH QUALITY) 12 □ One study with 170 adults showed that PEF variability (mean amp%highest >15%) has a sensitivity 13 of 0.03 and a corresponding	

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				specificity of 0.99 for diagnosing asthma in people presenting with 14 respiratory signs and symptoms. (HIGH QUALITY) 15 □ One study with 61 children and young people showed that PEF variability (mean amp%mean 16 >12.3%) has a sensitivity of 0.50 and a corresponding specificity of 0.72 for diagnosing asthma in 17 people presenting with respiratory signs and symptoms. (HIGH QUALITY) 18 □ One study with 74 children and young people showed that PEF variability (amp%mean >20% 19 versus PC20 histamine >16mg/mL) has a sensitivity of 0.46 and a corresponding specificity of 0.80 20 for diagnosing asthma in people presenting with respiratory signs and symptoms. (HIGH QUALITY) 21 □ One study with 74 children and young people showed that PEF variability (amp%mean >20% 22 versus bronchodilator reversibility change in FEV1 >10%) has a sensitivity of 0.71 and a 23 corresponding specificity of 0.58 for diagnosing asthma in people presenting with respiratory 24	

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				signs and symptoms. (HIGH QUALITY) **Recognising the validity of this approach – and in particular its very high specificity (negativity in health),.the GDG have included measuring peak flow variability in the algorithm for help in cases of doubt. What we fail to understand, given its negligible cost, and the ease with which this test can performed and repeated , why this is not recommended as the first line diagnostic assessment for providing objective evidence of reversible airways obstruction.** Here is the GDGs discussion of this *The PEF diary is currently a key tool in primary care, particularly in adults. It is a good test to rule in asthma in children over the age of 5 as well as adults, but it is subject to wider variability in clinical practice than it is likely to be seen in clinical trials and thus the applicability of trial evidence is perhaps limited.* The point that "it is subject to wider variability in	

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				clinical practice than in clinical trials" is likely to be equally applicable to all the tests analysed in the guideline: the key to improving this is … better education of health professionals. This has the air of special pleading against the validity and value of peak flow variability assessment in asthma diagnosis.	
Primary Care Respiratory Society UK	Full	14 15		**Skin Prick Tests and serum IgE Chapters 14 and 15** Clear analysis of the data and sensible conclusions.	Thank you for your comment.
Primary Care Respiratory Society UK	Full	16		**FeNO Chapter 16** The statement on FeNO testing in asthma diagnosis in the most recent BTS/SIGN guideline is Experience with .. FE_{NO} is limited to a few centres and more research	Thank you for your comment. The recommendation in favour of using FeNO as an aid to diagnosis is based on newer evidence. The FeNO sections in the BTS/SIGN guideline were not updated in the 2014 version. The NICE guideline provides a more recent review of the FeNO evidence. We agree that because the FeNO test can be affected by smoking status we have added a

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				needs to be done before any recommendations can be made. The emphasis on using FeNO in this guideline is a major change and it would be helpful for the document to clarify whether it is new evidence or a change in the interpretation of existing evidence that has led to the change in recommendation from the existing widely used and NICE approved British Asthma Guideline. Seventeen studies are analysed – the majority were conducted on groups of patients referred to secondary care clinics. Seven of the studies were cross sectional studies comparing FeNO with a reference standard, only one of which was done in an exclusively paediatric group. It is not clear whether any of the studies was conducted in a primary care setting. Nine of the studies were conducted in the last 5 years. The costings for FeNO testing do not include the capital cost of acquiring FeNO machines nor any associated staff training costs.	recommendation to reflect this. The prevalence of smoking in people with asthma is approximately 20% meaning that cigarette smoke will not affect the diagnostic accuracy of FeNO in 4 out of 5 people. This is a diagnostic guideline and smoking cessation is outside the remit of this guideline.

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				The GDG note some important potential factors that may make FeNo levels difficult to interpret : *FeNO levels can be altered by corticosteroids, smoking or previous smoking history and diet. The GDG excluded studies in which more than 50% of the population were taking corticosteroids, or if the smoking history of the population was unclear* The confounding effect of tobacco smoking is clearly of importance given the frequency of cigarette smoking in people presenting with respiratory symptoms and the imperfect reliability of patient reporting of smoking history. It is acknowledged that FeNO levels cannot on their own be used to make a diagnosis of asthma	
Primary Care Respiratory Society UK	Full	17		**Chapter 17 Peripheral blood eosinophil count**	Thank you for your comment.

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				Clear analysis of data and sensible conclusions	
Primary Care Respiratory Society UK	Full	18		**Chapter 18 Direct bronchial challenge test with histamine and methacholine** These tests are complex to perform, not available in primary care, not consistently available in secondary care clinics and only like to be performed once. After a complex analysis of their cost effectiveness in various places in a diagnostic algorithm their use is recommended by the GDG in persons over age 16 as part of a strategy to clarify the diagnosis in situations of inconsistent results from other diagnostic tests. It is acknowledged that these tests are expensive to perform and interpret. It is also acknowledged that *Bronchial hyper-reactivity varies over time so a negative test does not exclude asthma, therefore the test cannot be used to rule-out asthma on its own.*	Thank you for your comment. We agree with your comment about the current availability of bronchial challenge testing. It is not perfect, but it is the test with the best combination of sensitivity/specificity, and therefore is placed in the algorithm for use where there is genuine doubt after other testing. There is an implementation challenge to be met, but the GDG noted that the test is commonly used in other countries and believe that it should be used more often in the UK.

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Stakeholder comments table

28/01/2015-11/03/2105

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Primary Care Respiratory Society UK	Full	19		**Chapter 19 Bronchial challenge with mannitol** Clear analysis of data and sensible conclusions	Thank you for your comment.
Primary Care Respiratory Society UK	Full	20		**Chapter 20 Indirect bronchial challenge testing with exercise** The evidence base for these widely used tests is very weak and the GDG does not recommend them for adults and proposes research to investigate their use in children . However what is analysed her is evidence based on formal exercise testing in hospital with spirometry as the measurement. What is not considered is the quite widely used intervention of using exercise challenge within a period of peak flow monitoring – asking the patient to measure peak flow before and after exercise during the peak flow monitoring period . This can be a useful addition to a peak flow monitoring strategy in	Thank you for your comment. This suggestion was not made during the stakeholder consultation, and a specific search for this type of exercise challenge was not made. The GDG cannot immediately think of any formal analysis of this test.

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				diagnosis and may increase the sensitivity of peak flow monitoring for the detection of asthma.	
Primary Care Respiratory Society UK	Full	21		**Chapter 21 Diagnostic summaries** This chapter summarises the algorithm recommendations in verbal form. The recommendations do not make easy reading and the educational challenges in conveying this diagnostic approach to primary care professionals will be significant, and , we think a greater challenge than explaining the probabilistic model currently used in the BTS/SIGN guideline. The algorithms themselves do not align well with the descriptions of the diagnostic test in the text. For example, it is not clear from the text that FeNO is recommended as follow on to spirometry for virtually every patient in whom asthma is suspected. This only becomes clear in the algorithms. **The possibility needs to be considered that**	Thank you for your comment. We have sympathy with this view and suspect that the vast majority of clinicians will use the diagnostic algorithms rather than the verbal form of the recommendations. NICE recommendations are required to be written in verbal form and hence both formats of the recommendations are provided. We agree that the recommendations will require some change in practice, but we do not think that the diagnostic algorithm is prohibitively complex. Patients who present to their GP with mild symptoms of asthma can perform spirometry, BDR and FeNO tests in a follow-up appointment with the practice nurse to get a positive diagnosis of asthma. FeNO is new, and we agree that there is a cost to implementing this, but our economic analysis shows that including this is cost-effective. It is actually a very simple test to perform, easier than spirometry, and we would suggest that primary care will be glad to have access to this once the initial learning process is over. A small proportion of patients with

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				primary care practitioners' response to a diagnostic approach of this complexity will be to refer children and adults with suspected asthma to hospital services for diagnosis. The cost and logistic implications of this possibility require careful consideration. **A good recommendation to make here would be that anyone making a definite diagnosis of asthma should briefly summarise the evidence on which the diagnosis is based in a single entry in the medical records alongside the coded diagnostic entry.**	diagnostic uncertainty will go through the longer route in the diagnostic pathway in order to obtain further objective testing evidence of asthma. Regarding the last point on summarising the evidence for the diagnosis, the GDG agrees with this and has added this to the recommendation.
Primary Care Respiratory Society UK	Full	23		**Chapter 23 Monitoring – Symptoms scores and questionnaires**. This chapter conducts a careful analysis of the evidence base for the use of the various symptoms questionnaires in existence and acknowledges the moderate to very low quality of the evidence base for their usefulness.	Thank you for your comment.

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				CHILDREN (5-16 years) 7 □ No evidence was identified on mortality and unscheduled healthcare utilisation outcomes. 8 □ Monitoring asthma control questionnaires vs usual monitoring was considered a clinically 9 important benefit for QOL, asthma control questionnaire score and lung function (FEV1) at <6 10 months (evidence for all outcomes from 1 study, N=90, low and very low quality) 11 □ Monitoring asthma control questionnaires vs usual monitoring resulted in no clinically important 12 difference for QOL, asthma control questionnaire score, and lung function (FEV1), all at ≥6 13 months, and for symptom free days and ICS use, both at <6 months and ≥6 months (all evidence 14 from 1 study, N=90, low and very low quality). 15 □ Monitoring asthma control questionnaires vs usual monitoring resulted in an borderline clinically 16 important difference for exacerbations at ≥ 6 months (1 study, N=75, very low quality)	

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				ADULTS (>16 years) 18 □ No evidence was identified for mortality. 19 □ Monitoring asthma control questionnaires vs usual monitoring was considered a clinically 20 important benefit for QOL (2 studies, N=333, moderate quality), UHU (1 study, N=150, very low 21 quality), asthma control questionnaire score measured on the ACQ (1 study, N=183, low quality), 22 lung function and symptom-free days (both from 1 study, N=183, low quality), all at ≥6 months 23 and for use of rescue medication and <6 months and ≥6 months (low and moderate quality). 24 □ Monitoring asthma control questionnaires vs usual monitoring resulted in no clinically important 25 difference for Asthma control questionnaire score at < 6 months and ≥ 6 months measured on the 26 ACT (1 study, low quality) and for ICS use at ≥6 months (1 study, N=183, very low quality). 27 □ Monitoring asthma control questionnaires vs usual monitoring resulted in a borderline clinically 28 important difference for exacerbations	

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				(assessed with course of OCS) (2 studies, N=333, very low 29 quality) and exacerbations (assessed with ER, hospitalisation or course of OCS) (2 studies, N=333, 30 very low quality), both at ≥ 6 months. It is acknowledged that the recommendation to use these instruments is based largely on expert opinion : *The strength of the recommendation was based on the GDG opinion (not the evidence alone) that a questionnaire should be used to capture symptom and control information.* The recommendation for further research on the use of symptom control measures – including the RCP 3 questions currently included in the QOF – is sensible . This simple symptom score was adopted for the	

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				QOF because of its feasibility within the constraints of routine follow up in primary care and evidence from two studies suggesting its value. Gaylor Hoskins**1***, Brian Williams**2**, Cathy Jackson**3**, Paul D Norman**4** **and** Peter T Donnan**1** http://www.biomedcentral.com/1471-2296/12/105/ Assessing Asthma control in UK primary care: Use of routinely collected prospective observational consultation data to determine appropriateness of a variety of control assessment model Thomas M, Gruffydd-Jones K, Stonham C, Ward S, Macfarlane T**:** Assessing asthma control in routine clinical practice: use of the Royal College of Physicians '3 Questions'**.** *Primary Care Respiratory Journal* 2009, **18**(2)**:**83-	

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				88. PubMed Abstract | Publisher Full Text Feasibility is a key issue in recommendations for regular asthma reviews in primary care given the very large number of consultations involved and the time pressures under which this important task is conducted.	
Primary Care Respiratory Society UK	Full	24		**Chapter 24 Monitoring lung function tests** The evidence based is acknowledged as being of low quality and relevance. All the cited studies refer to the use of peak flow guided self management plans , not to health professional use of peak flow (or spirometry) data to monitor asthma control in follow up consultations. "Eleven studies were included in the review[3,23,28,37,38,77,90,96,169,180,187], ... All studies were of self-management, with the action plans based on PEF readings versus action plans based on symptoms."	Thank you for your comment. Regarding lung function monitoring in asthma review, no evidence was available to assess the utility of monitoring spirometry to measure asthma control. The consensus of the GDG was that spirometry provided significant additional information over and above PEF. Given the relative ease of monitoring spirometry and the additional information that it provides, the GDG felt that spirometry should be measured at every review. Spirometry provides additional information on the level of airways obstruction and can be compared to the previous best measurement or predicted measurement based on age and height of the individual. As no evidence was identified comparing PEF or spirometry monitoring by a GP at each asthma

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				In adults, for the comparison of monitoring PEF vs conventional monitoring, evidence ranged from very low to moderate quality. For the majority of the outcomes, evidence was only available from one or two studies. In children, all the evidence was of very low and low quality. For the majority of the outcomes, evidence was only available from one study and the studies were of small sample size. This seems a very weak evidence base for a recommendation with major implications for primary care namely to .. **36. Monitor asthma control at each review in adults and children aged 5 years and over using either spirometry (FEV_1) or peak flow variability.** The evidence base for recommending spirometry in this context is totally absent, and it is weak for peak flow monitoring. A period of peak flow monitoring (or spirometry) is feasible and potentially useful where problems of poor control	review, the GDG made a consensus recommendation on the basis of current best practice that either spirometry (FEV1) or PEF should be used at every asthma review to monitor asthma control in children aged over 5 years.

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				are identified – or where the diagnosis is under review- but there is no evidence base for mandating this as part of every asthma review.	
Primary Care Respiratory Society UK	Full	25		**Chapter 25 Monitoring – Fractional Exhaled Nitric Oxide** Here the analysis of evidence is clear and the recommendations for practice and research seem sensible , and are in line with the conclusion in the BTS/SIGN guideline that there was inadequate evidence to support routine use of FeNO measurement in monitoring asthma control. *37. Do not routinely use FeNO to monitor asthma control.* 38. Consider FeNO measurement as an option to support asthma management in people who are symptomatic despite using inhaled corticosteroids [This	Thank you for your comment.

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				recommendation is from Measuring fractional exhaled nitric oxide concentration in asthma (DG12) [2014]. *FeNO monitoring costs £77 - £87 per patient per year. It can also have a large impact on resource utilisation by increasing or reducing ICS usage. Given there was no strong clinical evidence that showed significant health benefits the GDG noted that FeNO monitoring was unlikely to be cost-effective as a routine management strategy for all people with asthma. However the GDG noted that in a specific severe sub-group of patients the health benefits could be much higher. Therefore in these people FeNO monitoring could be a cost-effective management strategy and therefore identifying this subgroup through research was the GDGs top priority.*	
Primary Care Respiratory Society UK	Full	26		**Chapter 26 Monitoring peripheral blood eosinophil count** Clear analysis of data and sensible conclusions (	Thank you for your comment.

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				no recommendation)	
Primary Care Respiratory Society UK	Full	27		**Chapter 27 Monitoring – challenge tests** Clear analysis of data and sensible conclusions **39. Do not use challenge testing to monitor asthma control.**	Thank you for your comment.
Primary Care Respiratory Society UK	Full	28		**Chapter 28 Monitoring adherence to treatment** The lack of evidence here is acknowledged: "We searched for randomised trials comparing the effectiveness of monitoring adherence with 2 feedback vs. no monitoring of adherence/usual care to guide asthma treatment and management. 3 Four studies were included in the review" The analysis here is limited by the fact that this is a very	Thank you for your comment. The purpose of this review was to investigate the clinical and cost effectiveness of monitoring adherence with feedback (i.e. using prescription/refill data, electronic monitoring inhalers, prednisolone level, MARS questionnaire FeNO levels, and theophylline levels to monitor asthma control) vs. usual care, and not whether or not monitoring should be done in the first place. The aim was to be able to make practical recommendations about best method(s) of measuring adherence, and the GDG shares your disappointment that it was not possible to recommend specific means of achieving this. The GDG has added bullet points to recommendation 1.3.1 to capture that adherence to

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				challenging area to study , that some review of adherence forms a universally accepted element of good practice in asthma reviews and that to omit this would be considered unethical . The 3 of the 4 studies involved using specialised devices to allow monitoring of compliance . The key research question is around how primary care practitioners can improve their assessment of and action on compliance difficulties. The limited recommendations in this key area seem disappointing . The vital importance of seeking to monitor adherence should be emphasised more strongly, despite the lack of published clinical evidence. *The GDG believed the uncertainty in the available evidence for all outcomes was sufficient to justify delaying a recommendation to await further research.* *The GDG considered that adherence to preventer treatment is an important area of asthma care and should be regularly monitored in all patients*	pharmacotherapy should be checked at every review and adjusted as necessary. This is in accordance with the Medicines Adherence clinical guideline CG76 and therefore the GDG has cross-referred to this guideline.

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				but … ***Recommendations*** ***Research recommendations*** ***4. What is the clinical and cost effectiveness of using electronic alert systems designed to monitor and improve adherence with regular***	
Primary Care Respiratory Society UK	Full	29		**Chapter 29 Monitoring inhaler technique** The evidence base is acknowledged as sparse and of low quality but sensible practice and research recommendations are made based on common sense and clinical experience.	Thank you for your comment.
Primary Care Respiratory Society UK	Full			**Chapter 30 Monitoring – telehealthcare** This chapter reviews the published evidence pertaining to a wide variety of telehealthcare	Thank you for your comment. The evidence was not sufficiently strong for the GDG to make a national recommendation in support of the use of telehealthcare to monitor asthma control; please see chapter 30 for the clinical and cost effectiveness evidence. However, the GDG made a future

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				interventions finding in the main evidence of moderate to poor quality *Four comparisons were considered for both adults and children:* *1) Tele-health services versus face-to-face equivalents;* *2) Tele-monitoring versus paper-based monitoring;* *3) Tele-health packages versus standard or usual care and* *4) Telehealthcare without healthcare professional involvement vs standard or usual care.* *Conclusions:* *Quality of evidence .* *In adults, the majority of the evidence was of low and very low quality for the critical outcomes. In children (with the exception of the carer QOL outcome in comparison 3 at moderate quality), evidence for all the critical outcomes was of low and very low quality. The evidence was downgraded due to risk of bias, imprecision and inconsistency.* *The GDG concluded that there was too little evidence and too much heterogeneity between interventions to support or refute the use of telehealthcare for monitoring asthma*	research recommendation to investigate the clinical and cost effectiveness of telehealthcare. The guideline recommendation does not prohibit use of telehealthcare (the GDG did not make a 'Do not' recommendation) if healthcare providers wish to make the capital investments in telehealthcare systems.

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				On one key question of the appropriateness of telephone as opposed to face-to-face review for asthma follow up *"the GDG did not feel they could make a recommendation concerning the replacement of face-to-face reviews with THC. "* This will disappoint those in primary care who are convinced that carefully managed telephone reviews have a valuable part to play in the safe and effective care of patients with asthma.	
Primary Care Respiratory Society UK	Full	General		There is no mention under monitoring of the importance of supporting patients in self management, nor of monitoring smoking status and behaviour. These are significant omissions.	Thank you for your comment. The prevalence of smoking in people with asthma is approximately 20%. Smoking cessation is outside the remit of this guideline and is provided in NICE public health guidance PH10, PH1, PH14, PH26, PH23, PH39, PH48, PH45 and PH5.
Primary Care Respiratory Society UK		641-2		The time taken for each proposed diagnostic procedure is listed in order to develop a cost for each test. The times required are proposed by NICE as follows: **Spirometry 20 minutes** (does this include	Thank you for your comment. The aim of the health economic component of this guideline was to identify whether spending NHS resources on additional test was a cost-effective use of resources, under the NICE reference case of £20,000 per QALY. An

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				interpretation? – no time is given for GP input, which is common) **Bronchodilator reversibility 20 minutes** **FeNO 10 minutes** Peak flow 10 minutes – train patient Peak flow 10 minutes – interpretation To implement the proposed algorithm involving spirometry, reversibility and FeNO would therefore require history taking, symptoms followed by 50 minutes – so a minimum 60 minute consultation in primary care. This would have considerable implications for primary care resourcing. It is worth noting that in the Support for commissioners guidance document for the Asthma Quality standard, the time allowed for a review consultation was 20 minutes. No time appears to have been assumed for a diagnosis consultation. (p13)	additional document, completed by NICE, which looks at budget impact will be completed and sent out with the final guideline. The cost of a diagnostic consultation was included in the model once the diagnosis was confirmed. The timings we used are on the generous side. Spirometry can usually be done in less than 20 minutes, FeNO in less than 10. Your comment also implies that in current practice asthma diagnosis can be made more swiftly. The currently used diagnostic method which is advocated by several stakeholders, but far less prominent in the proposed NICE pathway is a trial of treatment. However, this takes at least two visits, explanation of PEF measurement if this is used rather than symptoms alone, instruction in inhaler use, etc.
Royal College of	Full	General	general	The Primary Care Respiratory Society have submitted their response which is co-signed by me on behalf of the	Thank you for your comment.

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General Practitioners				RCGP (IR).	
Royal College of General Practitioners	Full	General	general	This guidance represents a big change in practice for a common condition and will raise many questions for GPs. Most of us will not have heard of FeNO nor be familiar with bronchial challenge testing. Implementing this complex diagnostic pathway will increase the number of appointments needed and present slight logistical challenges within surgeries such as using the new machines, which staff know how to do the tests. Therefore, it is likely to meet with much resistance, GPs will want to know why it's such a good idea. Questions which leap to mind are: What is different about someone diagnosed using these criteria? Different prognosis, treatment response for example. What do those diagnosed with existing methods have, if not asthma? Are those that are transient given a long term label? What are we to do with those who seem to have asthma clinically but don't pass the new tests? Would GPs refer all? Referrals will be going up significantly for bronchial challenge testing anyway. How are we to manage those with existing diagnoses if a third are overdiagnosed? Step down treatment, do all	Thank you for your comment. The primary aim of this clinical guideline was to produce the most clinically and cost effective way to diagnose asthma accurately. The GDG acknowledges that the implementation of some objective tests in primary care will require initial investment and training. However, the health gains and improvements in patient outcomes have been shown to be clinically effective as well as cost effective for the NHS; please see the health economic analysis in appendix M. The NICE Implementation team will produce support materials to facilitate uptake of the guideline into clinical practice. Furthermore, the GDG do not consider that all of the recommendations are new to clinical practice, for example, spirometry services should be available in all GP practices already. The only new objective test recommended in the guideline is a FeNO test, however, the GDG consider that performing a FeNO test is much easier than performing spirometry. FeNO has been shown to be cost effective by both the original health economic model developed as part of this guideline's cost effectiveness analysis and by the

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				these tests? We'll need to understand FeNO such as what variability in results? There could be chance of receiving a false positive during an acute episode, for example during hay fever season. The diagnosis flow charts are well designed and clear. It may help to engage GPs to clarify/estimate a reduction in the number of patients labelled with asthma (who then don't need to be over treated and over-monitored) and how we might go about undoing old incorrect diagnoses. The recommendation to use clinical judgement in the under 5s will fit well with most of our clinical experience. Navigating this age group through viral wheeze, bronchiolitis, hayfever and winter infections is inevitably complex and it's good not to be restrained by fixed rules here. It might be helpful to say a bit more about this though. Getting a more accurate diagnosis and avoiding harmful and wasteful overtreatment is indeed a good thing if this is what will be achieved but it will take a lot of	NICE DAP health economic model. Furthermore, the view of the patient members of the GDG is that patients want certainty of diagnosis before being put on life-long treatment. Regarding 'undoing old incorrect diagnoses', the guideline does not say that a review should be instigated in every single asthma patient's diagnosis. The diagnosis recommendations are for people under investigation for suspected asthma, not people with a diagnosis of asthma. Guidance on bronchiolitis in children will be provided in the forthcoming NICE clinical guideline due to be published in June 2015 http://www.nice.org.uk/guidance/indevelopment/gid-cgwaver136.

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				explanation and education and present challenges within practices (skills, appointments) and probably marked increase in respiratory referrals. (JT)	
Royal College of General Practitioners	Full	General	General	1. There are significant cost implications for primary care if we are to be asked to do so many spirometry reviews (and do we do a first spirometry and then rebook in for reversibility testing? (two costs included) Or, try and do it in one appointment. The costings from an RCGP / BMA perspective need consideration - costed at £9.50 - £14 seems very low compared with around £180 for a specialist spirometry (with metacholine), should be at fair amounts, and I am not sure that all the other costs are taken into account - recall / letters / communication etc. (light heating other overheads - otherwise we are spending 20x for twice the time and £5 worth of medication if it is done in a hospital). 2. The core test (spirometry) is based on 47 people in a trial of moderate quality, it seems rather strange to be with a sensitivity of 35% and specificity 100%. 3. The current guidance is based on a complex decision making process, but there is no evidence that this is better than the tests provided.	Thank you for your comment. Regarding point one the differential costs may arise due to the different setting in which the test is performed. The cost of spirometry in this guideline's economic analysis included the cost of all equipment used and healthcare professional time. The healthcare professional time, taken from the PSSRU, includes all the overheads regarding the setting. The costs derived in a specialist setting usually include other investigations therefore taking a much longer period of time and is performed most likely by an associate specialist. The £180 cost you cite is most likely for a challenge test as opposed to a single spirometry. There is a case for this test to be performed in primary care for a much lower cost however it is outside the scope of this guideline to recommend doing so. Spirometry is not advocated as a single test but as one element in the diagnostic algorithm. It is, of course, also part of the bronchodilator reversibility test. Regarding costs of BDR, your figures suggest

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				4. Bronchodilator testing appears to assume that the spacers are disposable (why) and one pMDI per person (£5 - they cost around £2) why are they for single patient use? 5. PF meter use seems to suggest a sensitivity of 56% and a specificity of 69% in the moderate trials. Are we happy to accept that 3/10 will be inappropriately diagnosed (this seems remarkably similar to the quoted over diagnosis rate)? 6. FENO in primary care as a diagnostic test on its own may be experimental and the evidence in highly selective people is not convincing. Think about the methodology used for selection into these trials and the sens / spec rates in the better quality trials. (Again we can do - but it needs careful costing as will be used regularly) 7. Monitoring - FEV1 meters and PEFR fine, all the RCP/ACT are okay and give us the funding very happy – but I have to confess a good communicator will pick up the non-compliance and the experienced thinking clinician will pick up the non-compliance and wrong diagnoses. This is not considered.	the costs of BDR testing will have been slightly over-estimated, and it should therefore still be cost-effective The most appropriate sensitivity and specificity for PEF variability found in the clinical review was 11% and 99% respectively. The guideline recommends that PEF should not be used on their own and only as part of a pathway. We do not agree that the FeNO papers were all conducted in highly selected subjects. The selection of papers was based on people with symptoms of possible asthma, exactly the population to which the guideline should be applied. Finally regarding non-adherence, many doctors think that they are good at picking this up, but the formal evidence suggest that in fact we are not very good at all.

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				(SH)	
Royal College of General Practitioners	Full	General	general	Whilst the Guideline Committee are to be congratulated on the production of this impressive document I remain very concerned, from an "ordinary GP" standpoint that there is such a strong guidance that measuring FeNO is a required component of diagnosis of asthma in Primary Care. As far as I can see, all the papers referenced for use of FeNO are from patients attending Secondary Care Clinics. Spirometry has not yet reached all primary care practices, and I am sure that FeNO measurement is only available in a handful of Primary Care practices throughout the country. There is thus a massive requirement for both Capital Investment in the purchase of equipment, and revenue implications for both training, maintenance etc which seems to have been completely ignored in the guideline. Quite rightly it is stated that Mannitol/methacholine challenge etc will need to be performed in secondary care, but it is assumed that the "compulsory" FeNO measurement following on from Spirometry will just be performed in Primary Care. (IW)	Thank you for your comment. The GDG acknowledges that FeNO testing in primary care is new and will require some initial investment. However, the best available evidence supports the clinical and cost effectiveness of FeNO and therefore the GDG considered the initial investment worthwhile for long-term patient health gains from increased accuracy in asthma diagnoses and reduced demand on NHS services, for example, preventable unscheduled healthcare utilisation. FeNO is an extremely simple test to perform and could certainly be done in primary care.
Royal College of Nursing	NICE	General	General	Whilst agreeing that there may be a misdiagnosis of asthma. We feel that in	Thank you for your comment. There is no gold standard asthma test, and as you point out FeNO, like other tests, is not completely accurate. For that

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				some cases this guideline does not adequately address the issues or makes diagnosis any easier. There are issues around the diagnosis. As an evidence based guideline we find very little robust evidence for the use of fractional exhaled nitric oxide (FeNO) as a necessary part of the diagnostic criteria. The original NICE technology appraisal of FeNo had statements referring to the fact that it is hard to estimate the relative diagnostic accuracy of FeNo and a difficulty in identifying the optimal cut off point for sensitivity and specificity. Of the 4 studies looked at, the cut-off point was between	reason the guideline suggests using the tests in combination. The detailed justification for including FeNO in this diagnostic pathway is given in chapter 16 of the guideline.

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				20ppb and 47ppb with a sensitivity of between 32-88%. The NICE Technology Appraisal recognised the variability in correlation between devices and the devices are noted to be definitely not interchangeable. NICE guidelines stipulates that a negative result does not exclude asthma and that there is no evidence of accuracy in the older population.	
Royal College of Nursing	NICE	General	General	There appears to be no recognition in this draft guideline of the fact that peripheral blood eosinophilia is the best predictor of a response to inhaled corticosteroids.	Thank you for your comment. The questions addressed by the guideline are how best to diagnose and monitor asthma, not how best to predict a response to inhaled steroids.
Royal College of	NICE	Gen	Gener	If diagnosis is problematic in primary care	Thank you for your comment. Please see section 11.4 on page 91 (consultation version, or page 92

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Nursing		eral	al	then the addition of spirometry to testing will complicate matters. If we cannot get the basics right; how will we train on machines that are not in place. It would be helpful to see the economic costing for this additional equipment and indeed the training requirements for its use.	final version) of the full guideline, and appendix M for the economic analysis. Spirometry should be available in primary care irrespective of this guideline. It has been recommended for several years in the NICE guideline on COPD.
Royal College of Nursing	NICE	Gen eral	Gener al	We feel the guidelines fail to acknowledge that the best person to diagnose asthma is a professional who is expedient in that area of health.	Thank you for your comment. It may be true that an experienced physician is better at many things than an inexperienced one, but the question is whether an experienced physician using objective tests to aid the diagnosis of asthma does better than the same physician without access to the results of objective tests.
Royal College of Nursing	NICE	9	1.3	Monitoring Asthma Control: The Asthma Control Test (ACT) can be used with children and their parents.	Thank you for your comment.
Royal College of Pathologists	Full	Gener al	General	The Royal College of Pathologists does not wish to be involved in this project.	Thank you for your comment.

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Royal College of Physicians	FULL	General	General	RCP wishes to endorse the comments submitted by the British Thoracic Society. The RCP is grateful for the opportunity to comment on the draft guideline. In doing so, we wish to fully endorse the comments submitted by the British Thoracic Society and bring attention to the following concerns raised by the RCP GP Network. The RCP GP Network find the draft a surprising departure from existing guidance; particularly in primary care focusing on the diagnostic use of spirometry and the use of fractional exhaled nitric oxide test (FeNO) in all candidates for ruling in or ruling out a diagnosis of asthma. Spirometry is well accepted and used in COPD diagnosis and management in primary care but the workload of assessing all new possible asthmatics has not been considered. We believe that the use of the FeNO test is largely unknown in primary care outside research studies or corporate sponsored (free) use. Although the cost of the test is said only to be £10, presumably including hardware(?), we have concerns regarding who will pay for this? We do not believe that practices will purchase the kit or consumables without NHS funding. The FeNO test looks like a very useful test in primary	Thank you for your comment. Spirometry is already advised as part of the initial assessment of an adult with suspected asthma in the BTS/SIGN guideline and therefore we would argue that this should not be regarded as a major change. FeNO testing is new, and the GDG acknowledges that there will be an implementation issue to address, but the detailed clinical and cost-effectiveness analysis described in the guideline shows that introducing this will be beneficial.

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				care. It has a very high sensitivity which means it is a very good rule out test which is usually what is needed. In secondary care rule in tests are often of more value but this test has a low specificity which determines how good a rule in test. The rest of the guideline is felt to be non-contentious, if complex. As such, we believe that it will be difficult to roll out in primary care without careful implementation.	
Scottish Intercollegiate Guidelines Network (SIGN)	Full/NICE/appendices	General	General	The SIGN/BTS British Guideline on the Management of Asthma, which is applicable to the whole of the UK, currently includes sections on the diagnosis and monitoring of asthma. This SIGN/BTS guideline is supported by Asthma UK, the Royal College of Physicians, the Primary Care Respiratory Society and Education for Health. It is also the basis for the NICE quality standard for asthma. The diagnosis and monitoring sections, along with a number of others, are due to be updated in 2015-16 as part of the regular biennial review of the guideline and publication of the revised guideline is expected in the summer of 2016. The Steering Committee for the SIGN/BTS asthma guideline is concerned that publication of the NICE	Thank you for your comment. The GDG does not feel that the recommendations on diagnosis in the NICE guideline are vastly different from that of BTS/SIGN, although we agree that the NICE guideline provides more detail of when to perform certain objective tests.

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				guideline on the diagnosis and monitoring of asthma could cause confusion amongst healthcare practitioners and patients alike due to differences in recommendations and, of particular concern, differences in diagnosis algorithms, between these two separate pieces of national guidance. This is clearly something we would wish to avoid. Specific clinical concerns of guideline development group members have been addressed separately through individual submissions or submissions on behalf of other stakeholder organisations.	
South eastern Hampshire CCG	Full	General	General	Re Diagnosis-- the use of FeNO is general practice is not widespread and certainly in our area it is a test done solely by the hospital specialists and mainly in adults. I would worry that a guideline that suggests a testing schedule that is so far removed from what is actually being done in primary care, will either be ignored by most or result in large amounts of referrals into secondary care for diagnosis . This has the potential to result in significant costs to health economies at a time when most are struggling anyway.	Thank you for your comment. The GDG acknowledges that FeNO testing in primary care is new and will require some initial investment. However, the best available evidence supports the clinical and cost effectiveness of FeNO and therefore the GDG considered the initial investment worthwhile for long-term patient health gains from increased accuracy in asthma diagnoses and reduced demand on NHS services, for example, preventable unscheduled healthcare utilisation. FeNO is an extremely simple test to perform and certainly can be done in primary car once the

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				It would seem to me that the diagnostic flow charts presented are at best aspirational but unlikely to get widespread acceptance or take up on the ground in primary care. Commissioners would have to think about provision of the FeNO testing kits and provide training to all practices and I would be surprised if this was considered a priority at this time.	equipment is in place.
South eastern Hampshire CCG	Full	General	General	re Monitoring- the numbers of asthmatics already in the community represent a major challenge to primary care to get reviews done. I would fully accept that a lot of reviews are not very good. Trying to get a record of PEFR variability from all would be a major challenge when it is difficult to get many asthmatics to attend at all. Our local experience is that the asthmatics you most want to review - ie those using ventoilin regularly and not taking prophylaxis are the most reluctant to attend appointments - it would be probably better for the population overall to develop truly practical ways	Thank you for your comment. The remit of this clinical guideline is to provide guidance on the best clinical practice. Implementation of the guideline is outside the remit of this clinical guideline. The NICE Implementation team will produce support materials such as costings tools to facilitate uptake of the guideline into clinical practice.

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				of getting patients in for review rather than making a review even more unlikely to happen . The sheer numbers of patients are overwhelming and to get spirometry done on all would be at best impractical - it is difficult enough just getting the COPD patients checked. Also a spirometry reading in an asthmatic does not really indicate what their symptoms are.	
The Anaphylaxis Campaign	Full	14	1.1.1	What is not addressed here and is essential in all patients with asthma is to take an **allergy focused history in relation to the asthma** to identify or exclude triggers. This should be a key recommendation in every patient. Most asthma in children and young adults is driven by allergy and in some cases avoiding the asthma trigger or introducing prophylactic therapy at appropriate times lead to complete resolution on the asthma symptoms. Examples include: seasonal asthma at the same time every year such as grass or tree pollen; seasonal asthma at the end of July often causing severe attacks which can lead to A&E attendance and hospital admission caused by allergy to alternaria. These can be prevented by introducing inhaled steroids at the correct time of year before the onset of asthma. Asking the right questions can pick up this recurring pattern easily. Identifying when asthma is driven by	Thank you for your comment. The remit of the guideline was to consider the best way of establishing a diagnosis of asthma per se, and then the best way of monitoring control whereas the issues you mention around allergen avoidance and seasonal adjustment of inhaled steroids are part of management of asthma. Nonetheless, we have included recommendation 1.1.4 which clearly advises taking a history of symptom triggers.

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				allergy has an obvious economic impact including: reduced admissions; reduced A&E attendance; reduced medication costs as well as improved quality of life. Publications to evidence this include "Alternaria Asthma" by S Nasser, T Pulimood. One trust reports about 30 acute asthma admissions in one weekend which were due to allergy. These could have been prevented had an allergy focused clinical history been taken and doing so can easily be achieved in primary care. This is part of asthma phenotyping and should be made more universal to improve patient outcomes and reduce cost to the NHS. Expert opinion also shows the value of allergen avoidance for example can completely stop asthma in some patients (such as removing a cat).	
The Anaphylaxis Campaign	Full	14	1.1.4	Asking about the family history of atopy is valuable as it identifies those at risk of having allergic asthma which feeds into the comment on 1.1.1. However having an allergy focused history in relation to asthma	Thank you. There is a recommendation that a family history of atopy should be obtained. (1.1.4 in the NICE version).
The Anaphylaxis Campaign	Full	16	1.1.15	As "allergic asthma is the commonest type, is associated with atopy and usually develops in childhood or early adulthood" this recommendation is surprising and worrying. Allergic asthma should be diagnosed with allergy testing (skin prick test or serum specific IgE). It is essential these tests are carried out alongside the medical history of each patient taking into account the comments made on 1.1.1 above.	Thank you for your comment. Recommendation 1.1.15 does not directly concern allergy. We suspect that you mean 1.1.5. This simply states that a history of atopic disorders alone is insufficient to diagnose asthma and should be interpreted as part of the whole run of recommendations, which goes on to explain what additional objective tests should be used.

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The Anaphylaxis Campaign	Full	General	General	Other pathways and guidance makes clear the link between allergy and asthma including the Royal College of Paediatrics and Child Health pathway for children with asthma and the NICE diagnosing food allergy in children and young people in primary care and community settings guideline which singles out asthmatics as an at risk group.	Thank you for your comment.
The Anaphylaxis Campaign	Full	General	General	The National Board of Health and Welfare (Socialstyrelsen), a government agency in Sweden, Ministry of Health and Social Affairs, produces national guidelines. The Key Opinion Leaders and asthma guidelines are finalized for April 2015, but the draft version is available for public comments. A recommendation is: The use of focused allergy testing with blood test or SPT is strongly recommended to be included in all basic asthma diagnosis. The evidence grade is 2 of 10 (1 being highest) The references below guide the recommendation outlining the clinical advantage for 3537 patients in 4 studies. References: 1. Eigenmann PA, A-MM, O'B Hourihane J, Lack G, Lau S, Matricardi PM, Muraro A, Namazova Baranova L, Nieto A, Papadopoulos NG, Réthy LA, Roberts G, Rudzeviciene O,	Thank you for your comment.

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				Wahn U, Wickman M, Høst A. European Academy of Allergy and Clinical Immunology Section on Pediatrics; European Academy of Allergy and Clinical Immunology-Clemens von Pirquet Foundation. Testing children for allergies: why, how, who and when: an updated statement of the European Academy of Allergy and Clinical Immunology (EAACI) Section on Pediatrics and the EAACI-Clemens von Pirquet Foundation. Pediatr Allergy Immunol 2013; Mar;24 ((2)):195-209. 2. Hoffmann-Petersen, B, Host, A, Larsen, KT, Bergstein, KR, Thomsen, ML, Braendholt, V, et al. Prevalence of IgE sensitization in Danish children with suspected asthma. Pediatr Allergy Immunol. 2013; 24(8):727-33. 3. Whitney D. Arroyave, M, Felicia A. Rabito, PhDb, and John C. Carlson, PhD, MDb. The Relationship Between a Specific IgE Level and Asthma Outcomes: Results from the 2005-2006 National Health and Nutrition Examination Survey. J ALLERGY CLIN IMMUNOL: IN PRACTICE. 2013; 1(5):501-8. 18 4. Matsui, EC, Sampson, HA, Bahnson, HT, Gruchalla, RS, Pongracic, JA, Teach, SJ, et al. Allergen-specific IgE as a biomarker of	

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				exposure plus sensitization in inner-city adolescents with asthma. Allergy. 2010; 65(11):1414-22. 5. Wang, J, Visness, CM, Calatroni, A, Gergen, PJ, Mitchell, HE, Sampson, HA. Effect of environmental allergen sensitization on asthma morbidity in inner-city asthmatic children. Clin Exp Allergy. 2009; 39(9):1381-9	
The National Allergy Strategy Group	Full	62		What is not addressed here and is essential in all patients with asthma is to take an **allergy focused history in relation to the asthma** to identify or exclude triggers. This should be a key recommendation in every patient - it is much more important than, and thus should have priority over, 'asking about a personal and family history of atopic disorders' (recommendation 7.6) Most asthma in children and young adults is driven by allergy and in some cases avoiding the asthma trigger or introducing prophylactic therapy at appropriate times lead to complete resolution of the asthma symptoms. Thus identifying allergy as one of/the trigger for asthma has clinical value and economic impact by providing either improved control or stopping asthma. There needs to be some knowledge of allergic triggers for asthma. Examples include: seasonal asthma at the same time every year such as grass or tree pollen;	Thank you for your comment. The remit of the guideline was to consider the best way of establishing a diagnosis of asthma per se, and then the best way of monitoring control whereas the issues you mention around allergen avoidance and seasonal adjustment of inhaled steroids are part of management of asthma. Nonetheless, we have included recommendation 1.1.4 which clearly advises taking a history of symptom triggers.

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				seasonal asthma at the end of July often causing severe attacks which can lead to A&E attendance and hospital admission caused by allergy to alternaria. These can be prevented by introducing inhaled steroids at the correct time of year before the onset of asthma. Asking the right questions can pick up this recurring pattern easily. However this rarely happens and instead admissions with acute asthma therapy occur at the same time in successive years. Identifying when asthma is driven by allergy has an obvious economic impact including: reduced admissions; reduced A&E attendance; reduced medication costs as well as improved quality of life. The value of this is well known in allergy practice Publications to evidence this include: Pulimood TB[1], Corden JM, Bryden C, Sharples L, Nasser SM. Epidemic asthma and the role of the fungal mold Alternaria alternata. J Allergy Clin Immunol. 2007;120(3):610-7 One trust reports about 30 acute asthma admissions in one weekend which were due to allergy to alternaria. These could have been prevented had an allergy focused clinical history been taken and doing so can easily be achieved in primary care. This is part of asthma phenotyping and should be made more universal to improve patient outcomes and reduce cost to the NHS. Expert opinion also shows the value of	

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				allergen avoidance: for example this can completely stop asthma in some patients (such as removing a cat). Suggest some specific questions are included, as for occupational asthma, eg does the asthma occur or get worse at the same time of year; are symptoms worse on exposure to furry animals; or to house dust eg after vacuuming or cleaning; are symptoms worse during the night or on waking etc. Once an allergy history identifies the likelihood of allergy, this can be confirmed by skin prick test or specific IgE serology (links to section 14 skin prick tests; and section 15 diagnosis specific IgE). .	
The National Allergy Strategy Group	Full	113		Asking about the family history of atopy may have some value as it identifies those at risk of having allergic asthma which feeds into the comment on 1.1.1. However having an allergy focused history in relation to asthma is the critical requirement.	Thank you. There is a recommendation that a family history of atopy should be obtained. (1.1.4 in the NICE version).
The National Allergy Strategy Group	Full	45		As "allergic asthma is the commonest type, is associated with atopy and usually develops in childhood or early adulthood" this recommendation is surprising and worrying. Allergic asthma should be diagnosed with allergy testing (skin prick test or serum specific IgE). It is essential these tests are carried out alongside the medical history of each patient taking into account the comments made on 1.1.1 above.	Thank you for your comment. Recommendation 1.1.15 does not directly concern allergy. We suspect that you mean 1.1.5. This simply states that a history of atopic disorders alone is insufficient to diagnose asthma and should be interpreted as part of the whole run of recommendations, which goes on to explain what additional objective tests should be used.
The	Full	113		Skin prick tests (or serum specific IgE) – note these	Thank you for your comment. The GDG agrees that

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National Allergy Strategy Group		120		comments do not refer to total IgE. The appropriate question to ask is what is the value of the skin prick test (or serum specific IgE) to a particular allergen such as grass pollen in a patient with asthma where testing is appropriately directed eg asthma to grass pollen allergy is suspected from the history; or similarly to house dust mite where perennial asthma triggered by house dust mite allergy is suspected from the history; is suspected form the history. These tests can *only be interpreted in the light of the clinical history*. Used properly they are of very considerable value – the allergy focussed history to elicit the triggers for asthma plus focussed skin prick test (or specific IgE). The tests in isolation are not useful. The tests inappropriately applied, where the diagnosis is 'asthma', but is not further refined by an allergy history, are less useful, because these test can indicate 'sensitisation' (positive tests without consequent allergy) as well as 'allergy' (positive tests with clinical allergy). Studies where the tests are not clinically targeted are not going to yield relevant answers on the value of these tests. The conclusion and recommendation 15.6 'that skin prick tests are not of value' is incorrect as it is based on studies which were inappropriate. These tests will identify particular subgroups of asthma eg house dust mite allergic asthma and play an essential role in phenotyping	allergy testing to aeroallergens to identify triggers is important and has added a recommendation to reflect this. The diagnostic accuracy of allergy tests to diagnose asthma was not supported in the review of the best available evidence.

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				asthma and improving standards of care. Unfortunately the important role of allergy in asthma is not highlighted sufficiently, nor recognised sufficiently, significantly weakening this guideline. The point of this comment is supported by a recent letter to the Lancet ***Lancet Respir Med* 2015** Published **Online** March 6, 2015 tp://dx.doi.org/10.1016/	
The National Allergy Strategy Group	Full	113 120		Expert opinion supports the above comment (number 4) and cannot be ignored. However there are some studies to support this. For example, the clinical sensitivity and specificity of specific IgE to inhalant allergens derived from 5170 comparisons with clinical diagnosis were 89% and 91 %, respectively (836 cases). 24% of the patients in this study had asthma. Paganelli R, Ansotegui IJ, Sastre J, Lange C-E, Roovers MHWM, de Groot H, Lindholm NB, Ewan PW. Specific IgE antibodies in the diagnosis of atopic disease. Clinical evaluation of a new *in vitro* test system, UniCAPi^", in six European allergy clinics. Allergy 1998: 53: 763-768	Thank you for your comment. The GDG agrees that allergy testing to aeroallergens to identify triggers is important and has added a recommendation to reflect this. The study referred to assesses the accuracy of IgE for diagnosing atopy. The diagnostic accuracy of allergy tests to diagnose asthma was not supported in the review of the best available evidence.
The National Allergy Strategy	Full	86	1.1.9	Spirometry is a better tool than PEFR and is available in primary care so should be the recommended measure in primary care.	Thank you for your comment.

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Group					
The National Allergy Strategy Group	Full	130	1.1.16	Exhaled NO. This is a useful tool but is not appropriate for primary care. It should be used in secondary care at the discretion of the consultant in respiratory medicine or allergy in selected and not all patients.	Thank you for your comment. Although there will be a requirement for education around FeNO for those unfamiliar with it, we see no reason why those in primary care should not be able to acquire these skills. FeNO is easier to perform than spirometry, and interpretation of results is no more difficult.
The National Allergy Strategy Group	Full	General	General	Other pathways and guidance makes clear the link between allergy and asthma including the RCPCH pathway for children with asthma and the NICE diagnosing food allergy in children guideline which singles out asthmatics as an at risk group.	Thank you for your comment.
The National Allergy Strategy Group	Full	113 120 General	General	The National Board of Health and Welfare (Socialstyrelsen), a government agency in Sweden, Ministry of Health and Social Affairs, produces national guidelines. The Key Opinion Leaders and asthma guidelines are finalized for April 2015, but the draft version is available for public comments. A recommendation is: The use of focused allergy testing with blood test or SPT is strongly recommended to be included in all basic asthma diagnosis. The evidence grade is 2 of 10 (1 being highest) The references below guide the recommendation outlining the clinical advantage for 3537 patients in 4 studies.	Thank you for your comment.

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The Royal College of Paediatrics and Child Health	NICE		13	This indicates using FeNO test in certain circumstances for 5-16 year olds. 1) This is not indicated in text on page 8 for diagnosing asthma although it does come on page 17 para 1.1.17. 2) This t is not available in paediatric departments at the moment, but we wonder about most GP surgeries. 3) Our contact, a respiratory paediatrician, does not regard this test as a priority when he cannot achieve having a respiratory nurse to assist him	Thank you for your comment. The text on page 8 relates to the key priorities for implementation; they are not the full list of recommendations. We sympathise your contact's desire to have the assistance of a specialist nurse, but this is specifically a guideline about the methods of diagnosing and monitoring asthma. Recommendations about personnel or other aspects of service delivery are outside our remit.

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				either in his hospital or the community. Could something go in about importance of nurse that knows about diagnosis and management of children?	
The Royal College of Paediatrics and Child Health	NICE	1	10	Diagnostic algorithm, which also applies to children, states 'do not use symptoms alone without objective test to diagnose asthma'. Earlier statements in document mention that objective tests have false positive and false negative; also such tests are difficulty in small children, especially under 5s.	Thank you for your comment. No objective test has 100% sensitivity and 100% specificity. The diagnostic algorithm provides the sequence of tests to use in combination to accurately diagnose asthma in children with asthma and to rule out asthma in children who do not have asthma. Please see recommendation 1.2.1 which states that a diagnosis of asthma cannot be made in children under 5 and that if asthma is still suspected when they are old enough to take part in objective tests they should be performed and the diagnosis reviewed.
The Royal College of Paediatrics and Child Health	NICE	1	10	Diagnostic algorithm discusses diagnosis in under 5s: based on observation and clinical judgement. The report of wheezing is part of the criteria to consider diagnosis of asthma but for toddlers many parents report as 'wheezing' when the child has upper respiratory rattles. This is a diagnostic pitfall which needs mentioning.	Thank you for your comment. Please see recommendation 1.2.1 which implies that a diagnosis of asthma cannot be made in children under 5 and that if asthma is still suspected when they are old enough to take part in objective tests they should be performed and the diagnosis reviewed.
The Royal College of Paediatrics and Child	NICE	1	13	Algorithm for children 5-16 years mentions use of peak flow variability over a few weeks; peak flow readings are technique dependant and operator effort dependant and can give false results. Algorithm should refer to pitfalls	Thank you for your comment. PEF variability has these problems, and that is one of the reasons it is not recommended as a sole test in children or in adults. On balance however, the GDG felt that it had

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Health				(what to look for) in peak flows. Also, how is 'variability of 20%' calculated – by a mean of peaks and troughs, or single occurrence of peak-trough or what?	some utility particularly as a rule-in test when positive. The method of calculating variability is to use the amplitude (highest minus lowest daily reading) divided by the highest reading, and then average this over the period of monitoring.
The Royal College of Paediatrics and Child Health	NICE	1.2.1	18	For under 5s guideline recommends considering tests for asthma (as for 5s and over) when they reach 5 years of age and if diagnosis still in place. Guideline should advise whether these tests are done whilst continuing current anti-asthma treatment (e.g. inhaled corticosteroids) and if so, is it same diagnostic criteria on tests as for those not on treatment. If treatment should be stopped before tests – for how long, and could it be dangerous to stop in some patients.	Thank you for your comment. The GDG has added bullet points to recommendation 1.2.1 to reflect how existing treatment should be managed when the child is able to perform objective tests.
The Royal College of Paediatrics and Child Health	NICE	1.3	21	The section on monitoring asthma control covers all ages (children and adults); there should be guidance that in many children asthma severity decreases with age and treatment can be decreased (and even stopped). Monitoring just to tick a box that asthma has been reviewed is pointless. Perhaps at each monitoring visit the doctor/nurse specialist should record that treatment should remain the same, be increased or be decreased.	Thank you for your comment. Guidance on stepping up and down asthma treatment is outside remit of this guideline but will be considered in the NICE guideline on management of asthma.

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The Royal College of Paediatrics and Child Health	NICE	3.1	24	The guideline states 'objective measures….can improve diagnostic certainty…'; is there evidence for this in the hands of normal primary and secondary care practitioners? The aim appears to be to reduce diagnosis of asthma when it's not present, but is there a risk of failing to diagnose asthma when present? If so, which is more dangerous?	Thank you for your comment. The primary aim of this guideline was to produce the most clinically and cost effective way to accurately diagnose asthma in people who do have asthma and to rule out asthma in people who do not have asthma. The sensitivities and specificities of objective tests reviewed were taken fully into consideration with this aim. The principle is to improve overall accuracy of diagnosis, and therefore to reduce under-diagnosis and over-diagnosis.
The Royal College of Paediatrics and Child Health	NICE	General		It is likely practitioners will use the algorithms with barely reference to rest of the document; it's important that pitfalls in the various steps of the algorithm are indicated on the same page (with reference to another page giving greater detail). Otherwise we risk going back to the days when asthma in children was under-diagnosed.	Thank you for your comment. We agree that users will rely mainly on the diagnostic algorithms, but it is not possible to give much more detail in these – they are already quite crowded and a number of stakeholders have commented on their complexity. The GDG believes that utilising these recommendations will improve the overall diagnostic accuracy in cases of suspected asthma, and not lead to an increase in under-diagnosis.
The Royal College of Paediatrics and Child Health	NICE	General		This document addresses only diagnosis and monitoring and does not discuss management. It does not appear to address the diagnostic difficulties in children under 5, who cannot perform PFR, spirometry or FeNO testing. For paediatricians, this is the most difficult group	Thank you for your comment. Asthma management is outside the scope of this guideline. NICE is currently scoping for a new guideline on asthma management.

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					We agree that diagnosis in the under 5s is particularly difficult. Please see recommendation 1.2.1 which states that a diagnosis of asthma cannot be made in children under 5 and that if asthma is still suspected when they are old enough to take part in objective tests they should be performed and the diagnosis reviewed.
The Royal College of Paediatrics and Child Health	NICE		15	They suggest spirometry as a routine diagnostic test for all children over 5 years. There are several problems with this: 1) teaching children to do spirometry reliably requires considerable time from a skilled professional, which will not be available in either primary or secondary care, even if equipment is available. 2) There is a real risk of it being done badly and being misinterpreted 3) The younger the child, the greater the diagnostic difficulty yet the less reliable the spirometry 4) In most, improvement in symptoms, physical signs or simple peak flow rate after inhaled brochodilator is enough to make the diagnosis 5) Conditions other than asthma which lead to a reversible drop in PFR in an otherwise well child are extremely rare	Thank you for your comment. We acknowledge the difficulties you describe. The GDG debated this at length but the paediatricians on the group felt that good readings can be obtained, particularly in older children, that the information is potentially valuable, and therefore that the measurement should be attempted. The important principle was that children should not have any less rigorous an assessment than adults, in those children able to comply with this.

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The Royal College of Paediatrics and Child Health	NICE		17	You advocate using FeNO testing in children over 5 where there is diagnostic doubt. This technology is not widely available at present even in specialist centres, and few people have experience in using it in children. It seems unlikely that clinicians in primary or secondary care will spend precious resources on this equipment when in the vast majority of cases the diagnosis can be made by simple means. In children, this technique should be reserved for the tiny number that require tertiary centre evaluation.	Thank you for your comment. We agree that FeNO testing is not widely available. The guideline sets out the clinical and health economic analysis which supports its role, which in essence is that it improves diagnostic accuracy. The GDG does not agree that the diagnosis of asthma can be made in the vast majority by simple means, if by this you mean that current practice cannot be improved. There is evidence of considerable misdiagnosis.
The Royal College of Paediatrics and Child Health	NICE		17	Bronchial challenge testing is unpleasant and hazardous and should not be used in children. This should be made clear.	Thank you for your comment. There is no recommendation for bronchial challenge testing in children.
The Royal College of Paediatrics and Child Health	NICE		16	Agree with the recommendations regarding the lack of any diagnostic value in skin-prick or blood tests.	Thank you for your comment.
The Royal College of Paediatrics and Child Health	NICE		21	Peak flow variability as a diagnostic method is limited by compliance. It is only of value if families do PFR monitoring reliably and regularly, which in my experience, most do not.	Thank you for your comment. PEF monitoring does require some effort and diligence. The test has value, particularly as a rule-in test when positive, and primary care representatives feel strongly about its continued use.

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The Royal College of Paediatrics and Child Health	General			This guideline does not contribute much that is of practical use in diagnosis and management of the majority of children with asthma. The advice in the existing NICE and SIGN guidelines is adequate. Although published evidence may support the use of spirometry and FeNO monitoring, using them in the real world is very different to a research study. If fully implemented, it would require a large increase in resources, both equipment and professional time, for very little benefit. Where GPs have a difficulty with diagnosis, it can nearly always be solved by a simple clinical assessment from an experienced secondary care clinician.	Thank you for your comment. The primary aim of this clinical guideline was to produce the most clinically and cost effective way to diagnose asthma accurately. The GDG acknowledge that the implementation of some objective tests in primary care will require initial investment and training. However, the health gains and improvements in patient outcomes have been shown to be clinically effective as well as cost effective for the NHS; please see the health economic analysis in appendix M. The NICE Implementation team will produce support materials to facilitate uptake of the guideline into clinical practice We appreciate the difference between research and real-world environments, but taking the implication of your remark to its logical conclusion would mean that no research should ever be translated into practice.
Thermo Fisher Scientific	Full	14	1.1.1	The draft guideline explicitly state[3] that clinicians should not offer skin prick tests to aeroallergens or measurement of serum total and specific immunoglobulin E (IgE) as diagnostic tests for asthma. This recommendation is **misleading, and potentially could be interpreted as being perverse and contradictory**, since later in the	Thank you for your comment. The remit of the guideline was to consider diagnosis of all asthma. Clearly when one wishes to differentiate allergic and non-allergic types one would have to do allergy tests, but that is not the question asked of the GDG. You suggest that a recommendation is "perverse

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				document the authors note that "allergic asthma is the commonest type, is associated with atopy, and usually develops in childhood or early adulthood".[3] The authors further note that atopy is defined as a genetic predisposition to produce IgE against common environmental aeroallergens, and that about 80% of people with asthma are atopic, compared with 30% of the general population. Such contrasting statements seem paradoxical: how can allergic asthma be diagnosed without the use of allergy testing? The reason cited for the recommendation to overlook allergy testing in the draft NICE guideline is its uncertain diagnostic accuracy. The ImmunoCAP blood test is the only fully quantitative measure of the presence of IgE, and is endorsed as gold standard by over 4,00 scientific publications. The presence of specific IgE as assessed by positive allergy tests alongside the occurrence of symptoms due to exposure to the specific allergen, indicates clinical allergy. Results of allergy tests therefore need to be considered alongside the medical history of each patient. For example, if a patient reports asthma only in the months of May and June and the results of allergy tests are positive for pollens from cypress, grasses, and ragweed, the cause of asthma	and contradictory" by comparing it against a sentence taken from one of the narrative sections of the guideline. This is an inappropriate comparison. It does not contradict other recommendations.

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				is clearly grass pollen because the other two plants have completely different pollination periods. Failure to combine data from medical history and tests can result in inappropriate treatment. http://dx.doi.org/10.1016/ S2213-2600(15)00089-2 Identifying when asthma is driven by allergy has an obvious economic impact including: reduced admissions; reduced A&E attendance; reduced medication costs as well as improved quality of life. Publications to evidence this include "Alternaria Asthma" by S Nasser, T Pulimooddoing so can easily be achieved in primary care. This is part of asthma phenotyping and should be made more universal to improve patient outcomes and reduce cost to the NHS.	
Thermo Fisher Scientific	Full	14	1.1.4	Asking about the family history of atopy is valuable as it identifies those at risk of having allergic asthma which feeds into the comment on 1.1.1. However having an allergy focused history in relation to asthma	Thank you. There is a recommendation that a family history of atopy should be obtained (1.1.4 in the NICE version).
Thermo Fisher Scientific	Full	16	1.1.15	As "allergic asthma is the commonest type, is associated with atopy and usually develops in childhood or early adulthood" this recommendation remains the priority.is surprising and worrying. Allergic asthma should be diagnosed with allergy testing (skin prick test or serum total and specific IgE). It is essential these tests are carried out alongside the medical history of	Thank you for your comment. Recommendation 1.1.15 does not directly concern allergy. We suspect that you mean 1.1.5. This simply states that a history of atopic disorders alone is insufficient to diagnose asthma and should be interpreted as part of the whole run of recommendations, which goes on to explain what additional objective tests should be

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				each patient taking into account the comments made on 1.1.1 above.	used.
Thermo Fisher Scientific	Full	General	General	Other pathways and guidance makes clear the link between allergy and asthma including the RCPCH pathway for children with asthma and indeed the NICE diagnosing food allergy in children guideline which singles out asthmatics as an at risk group. Testing for allergy using either SPT or SigE is recommended, based on an allergy focused clinical history, in both of these well respected guidelines. The National Board of Health and Welfare (Socialstyrelsen) is a government agency in Sweden under the Ministry of Health and Social Affairs, which give out national guidelines. The Key Opinion Leaders' asthma guidelines are finalised in April 2015, but the draft version is available for public comments. The use of focused allergy testing with blood test or SPT is strongly recommended to be included in all basic asthma diagnosis. The evidence grade is 2 of 10 (1 being highest) The references below guide the recommendation outlining the clinical advantage for 3537 patients in 4 studies. References:	Thank you for your comment.

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				1. Eigenmann PA, A-MM, O'B Hourihane J, Lack G, Lau S, Matricardi PM, Muraro A, Namazova Baranova L, Nieto A, Papadopoulos NG, Réthy LA, Roberts G, Rudzeviciene O, Wahn U, Wickman M, Høst A. European Academy of Allergy and Clinical Immunology Section on Pediatrics; European Academy of Allergy and Clinical Immunology-Clemens von Pirquet Foundation. Testing children for allergies: why, how, who and when: an updated statement of the European Academy of Allergy and Clinical Immunology (EAACI) Section on Pediatrics and the EAACI-Clemens von Pirquet Foundation. Pediatr Allergy Immunol 2013; Mar;24 ((2)):195-209. 2. Hoffmann-Petersen, B, Host, A, Larsen, KT, Bergstein, KR, Thomsen, ML, Braendholt, V, et al. Prevalence of IgE sensitization in Danish children with suspected asthma. Pediatr Allergy Immunol. 2013; 24(8):727-33. 3. Whitney D. Arroyave, M, Felicia A. Rabito, PhDb, and John C. Carlson, PhD, MDb. The	

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				Relationship Between a Specific IgE Level and Asthma Outcomes: Results from the 2005-2006 National Health and Nutrition Examination Survey. J ALLERGY CLIN IMMUNOL: IN PRACTICE. 2013; 1(5):501-8. 18 4. Matsui, EC, Sampson, HA, Bahnson, HT, Gruchalla, RS, Pongracic, JA, Teach, SJ, et al. Allergen-specific IgE as a biomarker of exposure plus sensitization in inner-city adolescents with asthma. Allergy. 2010; 65(11):1414-22. 5. Wang, J, Visness, CM, Calatroni, A, Gergen, PJ, Mitchell, HE, Sampson, HA. Effect of environmental allergen sensitization on asthma morbidity in inner-city asthmatic children. Clin Exp Allergy. 2009; 39(9):1381-9.	
UHL	Full	General	General	We agree with the guideline intent that the accurate diagnosis of asthma is an essential part of controlling asthma morbidity and mortality and improving the health of respiratory patients. However, we are not convinced that the guideline in its current format will achieve this aim. We have particular concerns about the use of fractional	Thank you for your comment. FeNO is recommended as one test which should be used in the diagnosis of asthma, and the guideline specifies that no objective test suffices on its own. Therefore we do not think that FeNO can be described as central to the guideline. The GDG acknowledges that FeNO testing in primary care is new and will

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				exhaled nitric oxide (FeN0) as a biomarker for the diagnosis of asthma. Interpretation of FeNO concentrations is not straightforward, even for specialist asthma physicians and we feel that there is very little evidence to support its use in primary care. Those studies that have used FeNO to guide management have generally been disappointing (1). We are not aware of any studies in primary care which have validated its use as a diagnostic tool that improves management. Despite this, while the guideline acknowledges the unreliability of exhaled nitric oxide (FeNO), it makes it central to the proposed diagnostic algorithm. In addition, there is no indication how the funding for the introduction of FeNO into primary care, in terms of the equipment and training, will be met. We also have concerns about some of the statements related to exercise testing, allergy testing, peripheral blood eosinophil counts and exercise-related symptoms that have been misinterpreted. Where there is low level evidence a negative statement has been produced which by itself is not supported by either the literature or established clinical practice. **Exhaled nitric oxide:** The evidence base for supporting the use of FeNO as a diagnostic test remains of low quality and insufficient to support its use in a diagnostic algorithm. The	require some initial investment. However, the best available evidence supports the clinical and cost effectiveness of FeNO and therefore the GDG considered the initial investment worthwhile for long-term patient health gains from increased accuracy in asthma diagnoses and reduced demand on NHS services, for example, preventable unscheduled healthcare utilisation. We also disagree that blood eosinophils have been "summarily dismissed". An evidence search was conducted against predetermined criteria, and the evidence was considered at some length by the GDG. We note that you do not cite any evidence to support the use of blood eosinophils in the diagnostic assessment of unselected people with suspected asthma, but rather quote its utility for other purposes (e.g. as a marker in severe asthma, which we do not dispute). We do not agree that an exercise induced fall in FEV1 is an integral part of the BTS stepwise management of asthma. We are confused by your assertion that exercise testing is used to exclude asthma in certain occupational settings because of its excellent specificity; a test with excellent

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				concentration of FeNO is affected by cigarette smoking, atopy, rhinitis and many other respiratory conditions. While these are discussed in the body of the guideline they seem to have been ignored in the diagnostic algorithms risking misinterpretation of the measurement. Although there is reasonable correlation between the sputum eosinophil count and FeNO there are so many discrepant patients that it cannot be reliably used in diagnosis and management, at least without further validation in a primary care setting. On top of this, international guidelines use a cut off point of >50ppb for a positive result. We are not therefore sure why the guidelines uses 40ppb introducing a significant chance of false positive results and encouraging over diagnosis of disease, the very thing the guideline is supposed to be tackling. Current evidence suggests that FeNO measurement is simply not accurate enough as a diagnostic tool. The guideline also fails to mention where the infrastructure and finance for the introduction for this testing process will originate. The guidelines will undoubtedly place further financial pressures on primary care to buy new equipment, train staff, upkeep and service the equipment and retain absolutely none of the proposed savings on medication spend that this is aimed to create. With primary care under increasing	sensitivity would be a better rule-out test. The detailed cardio-pulmonary exercise testing which you describe cannot be utilised in primary care which is where the vast majority of asthma diagnosis takes place, and where the other objective tests we recommend (with the exception of bronchial challenge) could reasonably be performed.

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				cost and workload pressure we cannot see this is deliverable without unnecessary imposition, which might be warranted if the evidence were in any way supportive, which it clearly is not. Spirometry and its interpretation is still often performed poorly in primary care, further leading to misdiagnosis, and we suggest that tackling this first before the introduction of an unproven and possibly inadequate test is critical. **Peripheral blood eosinophil count:** The reason for considering FeNO as a diagnostic marker is its association with a sputum eosinophilia which is a useful diagnostic marker as well as predicting risk of severe exacerbations and corticosteroid responsiveness (2-4). The best predictor of a sputum eosinophilia is a blood eosinophilia (5). It has also been known since 1975 that a blood eosinophilia is a risk factor for severe asthma and therefore offers added value over and above diagnosis (6, 7). In breathless patients a FBC investigation is merited to check for other causes such as anaemia and infection, and this single disease focus does not do the assessment of the respiratory patient justice. It appears to us somewhat bizarre that this very important investigation and relatively cheap test is so summarily dismissed. **Exercise testing:** Fall in lung function (FEV1) after exercise has been	

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				clearly shown to be a good predictor of both a raised sputum eosinophil count and responsiveness to ICS (8). It has also been an integral part of the BTS stepwise management of asthma and the evidence this is based upon. Whilst of low sensitivity it has excellent specificity and is the cornerstone for asthma diagnosis and exclusion in many occupational settings especially the Armed Forces and other uniformed services. Once again the use of poor to moderate standard research papers has led to the production of an unnecessarily negative statement in its use as a test for asthma, particularly amongst young active people. Certainly its specificity is much higher than FENO, spirometry, PEFR diaries and just about any other asthma test. In contrast Methacholine challenge testing which has a very high and useful negative predictive value has a significant degree of false positivity in young people and indeed has been excluded from acceptability by UK anti-doping for testing purposes in athletes who require proof of asthma as per previous WADA guidelines. The use of controlled cardiopulmonary exercise testing in the assessment of asthma, exercise-induced bronchoconstriction, dynamic hyperinflation and respiratory limitation all make the use of this test important, and the degree of negativity with respect to its diagnostic use is a poor representation of the	

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				evidence and does the guideline further harm. **Summary** In summary, the message from this guidance should be that GPs should refer patients for high quality diagnostics and phenotyping whenever there is doubt about the diagnosis, and in patients who respond poorly to treatment, i.e. patients who are not controlled at BTS/SIGN treatment step 3. If GPs follow the above advice on referral, and follow current BTS/SIGN asthma guidelines, stepping down treatment appropriately in stable patients, over-treatment and inappropriate treatment will be avoided. The guideline in its current form will not achieve this but increase confusion by using a poorly evidenced approach.	
United Kingdom Clinical Pharmacy Association Respiratory Group	Full	168	1	Please note: histamine is not licensed to test for airway hyper-responsiveness in the UK -NICE should clearly state this. This recommendation to use histamine should be noted as an off-label use of a licensed medicine via an unlicensed route of administration (in the UK, histamine is only licensed to treat AML as Ceplene® injection.	Thank you for your comment. The GDG agrees and has included histamine in the off-label footnote.
United Kingdom	Full	168	1	Obtaining pharmaceutical grade stock of the unlicensed medicines methacholine and histamine can be difficult,	Thank you for your comment. Guidance on procurement of agents such as methacholine and

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Clinical Pharmacy Association Respiratory Group				and we recommend that any guideline should suggest reliable sources of pharmaceutical grade stock.	histamine is outside the remit of NICE clinical guidelines. However, we will refer this issue to the NICE Implementation team to possibly be supported via the support materials they produce.
United Kingdom Clinical Pharmacy Association Respiratory Group	Full	168	1	Airway hyper-responsiveness is a complex test. Depending on the source of methacholine or histamine used, complex serial dilutions may be required to prepare the test, which involve a high risk of introducing errors due to mis-calculation and preparation errors. The guideline does not adequately consider this disadvantage, nor the advantage that mannitol is not subject to dosing errors.	Thank you for your comment. The GDG accept that few GPs are familiar with bronchial challenge testing, and that availability in secondary care is not universal. However, it is the single test with the best combination of sensitivity and specificity for diagnosis of asthma, and the GDG therefore concluded that it should be more widely used in this country. Regarding challenge testing with mannitol, please see chapter 19; the review of best available evidence did not support a recommendation for indirect challenge testing with mannitol but the GDG made future research recommendations to investigate the utility of mannitol challenge tests in both children and adults.
United Kingdom Clinical Pharmacy	Full	168	1	NICE should consider the lack of standardisation of practice for methacholine and histamine challenge tests due to the lack of standardisation of available preparations (as these are unlicensed medicines), and	Thank you for your comment. The GDG accept that few GPs are familiar with bronchial challenge testing, and that availability in secondary care is not universal. However, it is the single test with the best

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Association Respiratory Group				the variability of study methods reported in the NICE guideline. NICE should consider recommending a standardised approach to direct airway hyper-responsiveness testing	combination of sensitivity and specificity for diagnosis of asthma, and the GDG therefore concluded that it should be more widely used in this country. A comparison of different methods of performing bronchial challenge is beyond the remit of this guideline. The GDG suggest that results with different methods correlate closely, and it is more important that a unit has good internal quality control and uses a validated method, rather than imposing one method on all laboratories.
United Kingdom Clinical Pharmacy Association Respiratory Group	Full	172	18	The literature review of mannitol appears to be incomplete, as data is not included from Koskela et al Chest 2003;124:2171-7. Since this study (histamine vs. mannitol) is referenced in section 18 (histamine challenge tests), it should also be used for the mannitol section. Additionally, a Phase 3 study assessing mannitol as an indirect challenge test was not reviewed: Brannon et al. Respiratory Research 2005;6:144). This study reported relatively high sensitivity and specificity for mannitol of 88.7% and 95.0% in subjects not taking ICS).	Thank you for your comment. Regarding challenge testing with mannitol, please see chapter 19; the review of best available evidence did not support a recommendation for indirect challenge testing with mannitol but the GDG made future research recommendations to investigate the utility of mannitol challenge tests in both children and adults. Regarding the references referred to, the Brannan 2005 paper was excluded due to the population. The study recruits asthmatics and non-asthmatics, rather than the protocol population of suspected asthma with respiratory symptoms. In the study, non-asthmatics were required never to have had a

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					clinical diagnosis of asthma or experienced signs and symptoms suggestive of asthma. Studies of this design were excluded as they do not represent the population in which the test will be used clinically (people with respiratory symptoms) and inclusion of healthy controls may lead to over estimations of specificity. This paper was excluded during the first sift and therefore, does not appear in the excluded studies list. Koskela 2003 was excluded as it does not evaluate the diagnostic accuracy of mannitol for a diagnosis of asthma made by the reference standard, in the review population of people with suspected asthma. This study assesses the agreement between tests in people with already diagnosed asthma. We agree that the study was included in the review of the diagnostic of methacholine/histamine. However, this evidence was not used in decision making by the GDG, as it only provides the accuracy of histamine to predict a positive mannitol test in people with asthma. It does not provide the accuracy of histamine for the diagnosis of asthma in people with suspected asthma.
United Kingdom Clinical	Full	150	1	This guideline should consider to a greater extent the role of peripheral blood eosinophil counts as a marker of certain eosinophilic asthma phenotypes.	Thank you for your comment. Please see chapter 17 for the evidence review on the diagnostic test accuracy of peripheral blood eosinophils.

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28/01/2015-11/03/2105

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

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Pharmacy Association Respiratory Group					
Oxford Centre for Respiratory Medicine	Full	General	General	We agree that there is a large unmet need in the diagnosis and monitoring of asthma worldwide[1] and peer-reviewed guidance is essential to improve the morbidity and mortality associated with this common chronic lung condition. The new NICE guidance reflects that asthma diagnosis is multifaceted, as a consequence of airway dysfunction, remodelling and airway inflammation[2]; and we champion a change in current practice both across primary and secondary care. However, it is quite usual in the diagnostic work-up of airway disease, be it allergic or non-allergic asthma with variable or fixed airflow limitation, to gather all available evidence, using the pre-test probability to interpret results, select further diagnostics, introduce therapy or to decide whether a test needs to be undertaken[3]. By evaluating the sensitivity and specificity of specific symptoms and diagnostics individually, as has been performed in this guidance, we are left with a format that is	Thank you for your comment. We have sympathy for the concept of estimating pre-test probability, but we are unaware of any studies which consider different diagnostic strategies in people with different pre-test probabilities of asthma. We also acknowledge your concern about the risk of down-grading some facets of careful clinical assessment, but as you go on to say, the best predictors of inhaled corticosteroid response are objective measures of airway inflammation, and the GDG felt it had to include a test which reflects this. The Wagener paper which you quote shows that blood eosinophilia is the best predictor of sputum eosinophilia, not the best predictor of asthma, and the population studied had established diagnoses of asthma rather than being an unselected group with suspected but unproven asthma. In any case, this paper was published in 2015 and it misses the cut-off date and for inclusion in the guideline.

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				removed from current clinical practice and concerned that there will be patients with asthma that have a delay in diagnosis and treatment. The recent BTS/SIGN guidelines[4] advocate aligning patients with symptoms into those with a high pre-test probability, where a trial of treatment instituted, those with a low-test probability where an alternative diagnosis is sought and those with an intermediate probability where diagnostics such as FeNO and bronchial challenge testing could be useful. We are concerned that the new NICE guidance disempowers and discourages clinicians, early on in the diagnosis pathway, from taking into account the utility of both an atopic history, an exercise related history in a patient with a myriad of characteristic symptoms, and thus a high test probability, to diagnose a patient that is likely to respond to corticosteroid therapy. Whilst we agree that mandating FeNO is performed in the new draft guidelines for asthma diagnosis, thereby informing both clinicians and	

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				patients about the degree of corticosteroid responsive airway eosinophilic inflammation[5], we are concerned that the guidance does not infer that whilst this is a simple test to use, its interpretation requires specialist skills. There is no record in the guidance, nor within the designed algorithms that FeNO has to be interpreted with caution in smokers[6], or how it can be elevated in patients with rhinitis[7] or atopy[8] without asthma. The new draft guidance allocates a FeNO of 40ppb, which is not representative of previous recommendations[9] and does not seek for early specialist input in those with indeterminate results. Furthermore, it will undoubtedly not detect the phenotype of asthma that have neutrophilic inflammation[10] We were surprised that the draft guidance asks that a blood eosinophil count is not measured at any point in the diagnostic algorithm. This is a simple, minimally invasive, widely measured, interpreted and studied marker in airway disease; predictive of exacerbations[11], response to corticosteroids[12] and mortality[13]. It's omission from	

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				the guidance, despite its sensitivity and specificity being equal to that of FeNO, and better than that of PEF variability in the diagnosis of asthma is a concern. FeNO is a surrogate measure of eosinophilic airway inflammation[14] and the most sensitive and specific measure of eosinophilic airway inflammation is a blood eosinophil count, found to recently be more superior than FeNO alone in the diagnosis of asthma[15]. FeNO will measure one aspect of inflammation in the diagnosis of asthma; however, measurement of the peripheral blood eosinophil count as part of a full blood count (FBC) also clinicians to also exclude other causes of breathlessness which should be part of the clinical work-up. To summarise, we would advocate that clinicians use the pre-test probability to determine a diagnosis of asthma; and in patients with an indeterminate or low probability, specialist referral for complex diagnostics and phenotyping is mandated for diagnosis and/or management.	

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