Asthma diagnosis

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Action on Smoking and Health	Short	13	general	We strongly urge that consideration is given to including smoking as a trigger and risk factor to address in monitoring a person's asthma. Between 2012 and 2013 28% of people who died from asthma were current smokers or exposed to secondhand smoke. (Why asthma still kills: The National Review of Asthma Deaths (NRAD). Royal College of Physicians, 2014) People with asthma who smoke are more likely to be hospitalised and to have more symptoms than those who don't. (Thomson N. Chaudhuri R and Livingston E. Asthma and cigarette smoking. European Respiratory Journal 2004; 24: 822-833.) Recent evidence also points to the impact of parental smoking in the home on childhood asthma and that reducing exposure can have an impact on symptoms. (Burke H, Leonardi-Bee J, Hashim A, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. Pediatrics 2012; 129 (4):735-44.) Reference in this guidance to existing NICE smoking cessation guidance would provide important prompt for health professionals to address smoking among patients with asthma as a core part of the treatment pathway. In due course it would also be appropriate to reflect guidance on indoor air pollution currently in development. For further information on the relationship between smoking and asthma and the current evidence base see ASH research report: http://ash.org.uk/download/ash-research-report-asthma-and-smoking/	Thank you for your comment. We agree and have added this point to the recommendation.
Asthma UK	General			Asthma Diagnosis – use of objective tests Asthma UK welcomes the emphasis within these guidelines on the use of objective tests in diagnosis, potentially reducing misdiagnosis of asthma. A lack of objectivity can result in under-diagnosis that leaves people with asthma without treatments, placing them at considerable risk. Trial by treatment (without objective measurements and adequate follow up) also has considerable impacts for people for whom alternative causes for their symptoms are overlooked, or taking potentially harmful and unnecessary medication. The cost to the NHS of misdiagnosis of asthma and the resulting inefficient use of drugs could be considerable. The current reliance on trial by treatment for asthma diagnosis is potentially both inefficient and wasteful, when it is apparent that around 40 percent of asthma patients do not respond to initial	Thank you for your comment. We agree that different patients may have different triggers, but tests for excessive airway variability and airway inflammation are relevant to all. The diagnostic algorithm is designed to be used at the time that people present with symptoms. In relation to the need for re-testing when symptomatic, we agree that this may be necessary in some patients who present when symptoms have already improved spontaneously, because objective tests may also have normalised. However, this is less likely with FeNO than with measures of airflow limitation. We agree that further research would be useful. The areas suggested in the guideline are broad and many research questions suggested in other documents are likely to be compatible.

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				treatment (Spear, Heath-Chiozzi and Huff, Clinical Trends in Molecular Medicine, 7(5), 1 May 2001, pp.201-204). The use of objective tests in these guidelines therefore constitutes a significant change for clinical practice for asthma diagnosis. However, we must also recognise the limited accuracy of the individual tests in this guideline, which fail to reflect that each person's asthma is unique with individual triggers. Greater prominence should be given to the variable nature of asthma and the importance of changes in inflammatory markers and airflow limitation (and symptoms) over weeks, months and even years. Tests at a single point in time might miss a diagnosis of asthma, putting patients at great risk. In the event of a history of asthma-like symptoms but normal results at the time of investigation, re-testing when symptomatic would be advisable. The evaluation of evidence for asthma diagnostic tests in these guidelines highlights the paucity of adequately accurate and acceptable tests to confirm or exclude a diagnosis of asthma or advise on successful treatment regimes. This presents the most significant problem for any guideline on asthma diagnosis and requires urgent research and development. The three-year European Asthma Research and Innovation Partnership produced a systematic review of the diagnostic tools, which could form the basis for useful research recommendations to improve future guidelines.	
Asthma UK	General			Implementation of the NICE guidelines on asthma The key barrier to improved outcomes for people with asthma has been a failure to implement successive guidelines. The publication of the NICE Asthma Diagnosis and Monitoring Guideline and NICE Asthma Management Guideline this October, with their recommendations of significant changes to clinical practice, represents a considerable opportunity to ensure effective implementation of high quality care and to improve outcomes for people with asthma. The Diagnosis and Monitoring Guideline suggests that changes with respect to how asthma is diagnosed are met through the sharing of diagnostic facilities across primary care via 'diagnostic hubs', a substantial change to current service delivery that has the potential benefit of allowing the sharing of skills and experience, which is so variable at present. We regret that the feasibility project undertaken for these revised guidelines only considered the views of sites from a clinical perspective, and did not take into account the perspective of people with suspected asthma, who will need advice and support about the process, timeline, and what to do if symptoms change while awaiting tests. Initial diagnosis is also a key time for the education	Thank you for your comment. The aim of the primary care implementation feasibility project was specifically to assess the impact and feasibility of adopting the technical diagnostic tests (spirometry and FeNO) recommended in the proposed asthma diagnostic guideline into primary care in response to stakeholder comments. We understand the importance of the experience of people with suspected asthma, however, the scope of the project was to prioritise concerns highlighted by stakeholders around training and equipment and these areas formed the focus of the report. Thank you for your suggestion; . We agree that the BTS/SIGN guideline covers these areas very well. It is not NICE policy to cross-refer to non-NICE guidelines. BTS/SIGN and NICE guidelines are developed using different methodologies. NICE and BTS/SIGN are considering how best to clarify advice for those aspects of asthma care not covered by the NICE pathway for asthma diagnosis and management. NICE and BTS/SIGN are also discussing a longer term solution and how we might bring the two guidelines together. Thank you for your offer of support.

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				of people with asthma, especially on self-management; an opportunity that is not reflected in these guidelines. To prepare people with asthma, healthcare professionals and commissioners for these changes requires a carefully considered, fully costed implementation programme. This might include guidance on how services manage the transition to new clinical practice. We would therefore recommend the key section in the short version of guideline, 'Putting this guideline into practice', is complemented with greater detail in the full version and accounts for the impact on people with suspected asthma. Additionally, there is an opportunity to make the guidelines more comprehensive through the use of signposting, particularly regarding a diagnosis of severe asthma. Signposting to other guidance accredited by NICE, such as the BTS/SIGN British guideline on the management of asthma (2016, SIGN 153), would enhance the utility of the NICE Diagnosis and Monitoring guidelines in areas that it currently does not cover, for example severe asthma, occupational asthma, treatment of acute asthma. Signposting to the BTS/SIGN asthma guidelines would still be consistent with the NICE Quality Standard for asthma (QS 25). Taken together, these changes would ensure that the guidelines are fit for purpose and that a process of system change around clinical practice can begin immediately. Asthma UK is keen to work with NICE to ensure the implementation of guidance for asthma is smooth and accounts for the reality of current practice and the views of people with asthma.	
Asthma UK	General			**BTS/SIGN guidelines on the management of asthma** The NICE guidelines on *Asthma Diagnosis and Monitoring* (and *Management*) represent a significant change in practice to the long-standing, NICE-accredited BTS/SIGN *British guideline on the management of asthma* (2016, SIGN 153).	Thank you for your comment. We agree that the NICE guidance will represent a change in practice, but not that great a change. BTS/SIGN recommend all the tests that NICE recommends, although the detail is not the same. The main difference is that BTS/SIGN suggests that they do not need to be applied when there is a high probability of asthma based on history and examination.
Asthma UK	Appendix Q	857 857	18-24 26-30	**Feasibility project – Appendix Q** Asthma UK welcomed the decision by NICE to undertake a feasibility project to understand the challenges to implementation and the utility of its guidelines. There are several key issues raised in the *Summary and conclusions* of the feasibility project, including: - diagnostic spirometry takes time to do correctly - the new competency recommendations create adoption issues around access to (and funding of) training but the importance of improving the quality assurance of spirometry nationally was recognised both for asthma and other respiratory conditions	Thank you for your comment. The adoption team are planning to develop an adoption support resource to share learning from the sites involved in the feasibility study to support those in practice responsible for implementing this guideline. We agree that spirometry may take a few minutes to do properly, but it has been part of the BTS/SIGN recommendations for many years so this is not a new issue. Spirometry was obstructive in 27% of those who were diagnosed with asthma in the feasibility study, and although this is a minority it is extremely useful information in a sizeable minority. The cost-effectiveness and cost impact analyses have shown that FeNO is worthwhile. Lack of confidence in the results is a different issue, and hard to combat unless people start to use it. Formal studies of FeNO do not suggest that users need lack confidence in it, and the few members of the GC who have started to use it find it very useful. Provision of bronchial challenge testing is a problem in many areas. We hope that it will be more widely provided in response to this guideline since it is the single most accurate test for the diagnosis of asthma.

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		858	2-4	- there is scepticism with spirometry picking up airway obstruction, as this only happens if the person is symptomatic at the time of testing … - the cost of FeNO devices and consumables is a barrier to implementation - lack of clinician confidence in specific FeNO devices to produce consistent results may present an adoption issue … - bronchial challenge testing is largely not available in secondary care making it difficult to refer patients for this when they reach the relevant part of the algorithm (quoted from Appendix Q, pp.857-8)	
Asthma UK	Full	198-209		**Monitoring** We note that beyond the initial diagnosis of asthma there is no guidance in the monitoring of asthma to ascertain whether someone has severe asthma or occupational asthma, nor how to respond to the presentation of acute asthma. In the absence of such guidance it is likely that existing guidelines such as the BTS/SIGN *British guideline on the management of asthma* will be used, which could be confusing given differences in areas covered in both guidelines. **Monitoring: Symptom scores and questionnaires** (Full, pp.198-209) The recommendation regarding validated questionnaires omits the RCP 3 questions on the grounds of a lack of RCTs (Full, p.209). Given the prominence of their use and link to the Quality Outcomes Framework, the validity of the RCP 3 questions could be the basis of a research recommendation. There could also be an opportunity for research on the validity of asking people with asthma to record their responses on digital technology to enable real-time monitoring.	Thank you for your comment. Severe asthma is outside scope. We have a recommendation on checking for occupational asthma. We have a recommendation saying to treat people who are acutely unwell but the detail of acute asthma management is outside the scope of this guideline. We agree that clinicians should look to other guidance on areas not covered by this guideline. NICE and BTS/SIGN are considering how best to clarify advice for those aspects of asthma care not covered by the NICE pathway for asthma diagnosis and management. NICE and BTS/SIGN are also discussing a longer term solution and how we might bring the two guidelines together. We agree, hence the GC made the research recommendation "What is the clinical and cost effectiveness of using validated quality of life questionnaires and the RCP 3 questions as tools to monitor asthma control in adults aged 17 years and over?".
		259		**Monitoring adherence to treatment** We welcome the high-priority research recommendation: What is the clinical and cost effectiveness of using electronic alert systems designed to monitor and improve adherence with regular inhaled maintenance therapy in people with asthma? This research recommendation could be amended to reflect emerging opportunities for the use of smart, connected inhalers to monitor adherence, explored in Asthma UK's two reports, *Connected Asthma* and *Smart Asthma*.	Thank you. This research recommendation is deliberately worded to allow inclusion of a wide range of potentially useful electronic systems, and it could encompass the research on connected inhalers that you describe.

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		268		Using a smartphone's Bluetooth connection, smart inhalers are designed to collect and send data from sensors monitoring medication use. They aim to help track the daily inhaler use of a person with asthma, usually via a linked health app on the user's smartphone, and send alert reminders to use the inhaler. The aim of research in this area will be to assess whether the use of smart inhalers reduces the rate of asthma attacks in a "real-world" randomised controlled trial. **Monitoring inhaler technique** We welcome the clarity of the recommendation on when to monitor inhaler technique (Full, p.268, line 28), and the high-priority research recommendation: 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 people with asthma? This research question could be altered to reflect the emerging, connected devices that could help to improve inhaler technique. For instance, the Inhaler Compliance Assessment (INCA) device is designed to provide integrated acoustic analysis measuring correct inhaler technique and dosing that can be reported back to healthcare professionals. Additionally, CapMedic sensors record how an inhaler is being used, helping people to understand their inhaler technique and provide suggestions for improvements when needed.	
		291		**Monitoring: Tele-healthcare** We welcome the high-priority research recommendation: What is the long-term (more than 12 months) clinical and cost effectiveness of using tele-healthcare as a means to monitor asthma control in children, young people and adults? Modalities of tele-healthcare can include telephone interview (healthcare professional involvement) and internet or smartphone-based monitoring support (no healthcare professional involvement).	Thank you. Studies of the NCA device would be possible within the current research question framework. This has been made deliberately general to allow any emerging technology to be included.

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Asthma UK	Full	40-42		**Diagnostic algorithms** **Risks of withholding treatment** As above, we welcome the emphasis on the use of objective tests. However, as noted throughout the guidelines, asthma is a variable condition, which has implications for safe practice particularly if treatment is not prescribed until an asthma diagnosis is confirmed through tests currently unavailable in primary care. The feasibility project showed an increase in the mean time from first presentation to asthma diagnosis from 35 days to 53 days (Appendix Q, p.843, line 12; see also p.844, Figures 2 and 3). Notably the feasibility project has focussed on responses from sites, which neglects the impact of the new algorithms on people with suspected asthma. We are concerned that there could be a reluctance on the part of clinicians and patients to embark on a lengthy diagnostic pathway with potential barriers of travel, cost and time preventing people from obtaining tests to confirm or deny a diagnosis of asthma. The benefit of an accurate diagnosis must be balanced against the risks of not providing treatment over this period and a reliance on tests such as spirometry that depend on the person to be symptomatic for a confirmed diagnosis. There should therefore be greater clarity in the algorithms (and the guidelines more generally) as to when treatment might be started prior to diagnosis and also what the process should be to confirm a diagnosis in these cases. In the event of a history of asthma-like symptoms but normal results at the time of investigation, re-testing when symptomatic would be advisable. **Algorithm A: Initial clinical assessment** (p.40) and s.4.2 **Initial treatment at presentation** (p.43)**.** We welcome the inclusion of initial treatment at presentation if someone is acutely unwell during the initial clinical assessment. However, a clinical assessment of symptoms and risk should be routinely carried out at each appointment to ensure that there is no undue delay to commencing treatment. Asthma symptoms may be a sign of poor control and undertreated inflammation, which carries an increased risk for someone with asthma to experience a life-threatening asthma attack. We strongly recommend that treatment is considered at diagnosis for all people with suspected symptomatic asthma and that algorithms are developed to safely deliver this while not ignoring the need for objective evidence of asthma being present. **Algorithm B: objective tests for children and young people aged 5 to 16** (p.41)	Thank you for your comment. We make it clear in rec 1.1.5 that people who are acutely unwell at presentation should be treated straight away. We have added a recommendation asking people to re-present if they become unwell whilst waiting for objective tests. For most people it is better to wait for tests to confirm the diagnosis before embarking on a lifetime of medication. We acknowledge that FeNO is not currently widely available in primary care, but asthma diagnosis needs to improve and we hope by recommending it in this guideline it will drive the necessary change in this service provision. In the feasibility study prior to guideline implementation, nearly 20% of patients received an asthma diagnosis at their first presentation i.e. before any tests or trial of treatment could have been performed. This immediate firm diagnosis is not possible in the proposed NICE process, and this inevitable lengthens the median time to diagnosis. To implement the algorithm sites need at least two appointments to complete the required assessments and tests. We agree that asthma is a variable disease. The diagnostic algorithm is designed to be used at the time that people first present.. If there is diagnostic uncertainty, people will undergo 2-4 weeks of peak flow monitoring, which will allow variable disease to be detected. Regarding your point about treatment compromising further testing, we agree and have added a recommendation to 'Be aware that that the results of spirometry and FeNO measurement may be affected in people who have been treated empirically with inhaled corticosteroids'. We agree. We agree; the GC has developed algorithms that recommend treating people who are acutely unwell, but to not commit them to a lifetime of medication without any objective indication of asthma.

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				Asthma is a variable condition. Spirometry and FeNO tests at any one point in time carry the risk of being unreliable and misleading. The pattern of symptoms and test results over time are likely to be more reliable. *Spirometry* We note the limited clinical evidence base presented for the recommended use of spirometry with only six studies reviewed (p.88, line 6). Only one study was deemed of moderate quality, while others were of low or very low quality with serious or very serious risk of bias (Full, p.91, Table 27). For children, only one study of low quality which had very serious risk of bias was considered. Therefore, the recommendations regarding spirometry, and particularly its position in the algorithms (B and C), appear to be based on very little evidence, as highlighted in the 'Quality of evidence' section of the recommendations (Full, p.95). There are also key issues raised in the feasibility project that have not been addressed in the algorithms or elsewhere in the guideline. As highlighted in the feasibility project, there are concerns over the difficulty of performing spirometry on children under 8 (Appendix Q, p.857, line 14) and one of the seven sites was sceptical about the use of spirometry to diagnose asthma (Appendix Q, p.849, lines 17-18). These concerns, if representative of broader practice, could easily undermine the acceptance and long-term use of the guidelines. Additionally, issues regarding 'access to (and funding of) [spirometry] training' (Appendix Q, p.857, line 19-20) are likely to be substantial and, if not addressed, could seriously risk implementation of the guidelines. See also Comment 5 re adoption issues raised in the feasibility project. *FeNO* Considering the current lack of availability of FeNO devices at primary care, practices will be forced to send people to secondary care to get a diagnosis, which could result in significant costs that have not been considered in the guideline. More importantly for people with suspected asthma, there could be a long period before diagnosis and treatment, which is potentially very unsafe. As with spirometry – the other key test in this algorithm – the practical implementation of guidance for FeNO could be undermined without a clear exposition of how common challenges should be overcome. *Peak flow*	We agree that spirometry is not the most sensitive test for asthma, hence a diagnosis of asthma should not be made on the basis of a spirometry test alone. We also agree that it would be useful to have higher quality studies, but the GC based its recommendations on the best available evidence. Because the presence of bronchodilator reversibility is a hallmark of asthma, the GC consider spirometry is a useful test and it would be wrong to omit it. It is a key test in the BTS/SIGN guideline so it is not a change in practice. We agree that performing objective tests in children may be challenging, hence the recommendation on what to do if the child cannot perform the test at that point in time. The GC acknowledge that currently spirometry service provision needs improving in some areas, which is what NHS England aims to achieve in its quality assured spirometry guidance. The current BTS/SIGN guideline on asthma also recommends spirometry so this is not a change from current guidance. We agree this guideline calls for a change in practice, however there is evidence to show that asthma diagnosis needs to improve. Whilst we acknowledge there will be initial upfront costs to be met, if implemented, the guideline will improve patient outcomes and is cost-effective to the NHS in the long-term; NICE's cost impact assessment projects a saving of approximately £14 million per year in England, before implementation costs. GC Regarding your comment on peak flow variability, the GC did not consider this test showed sufficient diagnostic accuracy to warrant recommending it first-line. The utility of peak flow variability has been assessed and positioned in the algorithm. However, there is nothing to stop clinicians providing this test at the same time as spirometry and FeNO. See above with respect to similar response regarding the variability of asthma, training for spirometry and availability of FeNO.

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				We note the issues raised in the feasibility project in relation to the use of peak flow (Appendix Q, p.852, lines 17-26) and the challenges associated with a test that 'relies on patient technique, effort and concordance with the frequency of readings' (Full, p.114). However, in light of the considerable period of the proposed diagnostic pathway and the variable nature of asthma, a peak flow reading from the time of presentation could speed up asthma diagnosis by enabling healthcare professionals to utilise these readings alongside those for spirometry and FeNO. In some cases, monitoring peak flow might also remove the need to have FeNO measured in children, again reducing the burden on primary care and/or secondary care. Use of a peak flow from presentation could also provide an opportunity to introduce a key tool for self-management. **Algorithm C: objective tests for adults aged 17 and over** (p.42) Similar issues noted with respect to Algorithm A and B regarding the variability of asthma, training for spirometry and availability of FeNO – all of which affect undertaking asthma diagnosis – are applicable to Algorithm C. *Direct bronchial challenge testing* There are concerns that practices will face the same 'dead end' as encountered by sites in the feasibility project (Appendix Q, p.852, line 28-29). This is concerning given that 14 of the 143 people who presented with suspected asthma during the project period reached this point in the algorithm. The lack of UK marketing authorisation for the direct bronchial challenge test with histamine or methacholine represents a notable barrier to implementation (Full, p.45. fn e). *Formatting* The diagnostic algorithms are likely to be used widely across primary care. We would welcome the final versions being properly formatted to ensure they are easy to read and print. Issues with formatting appear to have been experienced by sites as part of the feasibility project (Appendix Q, p.854, line 11-12).	The GC acknowledges that currently access to bronchial challenge tests is limited and have made a recommendation on what to do if a bronchial challenge test is not available. However, bronchial challenge is the single most accurate diagnostic test for asthma. The GC has tried to limit it to those patients who need it most. Recommending it in this guideline will hopefully drive the necessary change in service provision. Formatting: Thank you for your comments. We will reproduce the algorithms in a separate document which will be formatted to be easily read when printed.
Asthma UK	Full	16	27	There are also key areas not included within the NICE guidelines that are covered in the BTS/SIGN guidelines. For instance, with respect to diagnosis, the NICE guidelines deliberately do not cover a diagnosis of severe or difficult-to-control asthma (Full, p.16, line 27). Signposting to the BTS/SIGN guideline – similar to signposting in the NICE *Quality statement 11: Difficult asthma* in Quality Standard 25 – would improve the utility of the NICE guidelines on asthma diagnosis and ensure that severe asthma is considered as a possible diagnosis.	Thank you for your comment. As a result of the scoping process, a decision was made to exclude diagnosis of severe or difficult-to control asthma. Thank you also for your suggestion, but NICE guidelines do not cross-refer to non-NICE guidelines (NICE quality standards are different in this regard). Discussions about the 2 asthma guidelines have been held; however, due to differences in remit and methodology a collaborative guideline would not be currently possible. Notwithstanding this, the GC considers the recommendations in both guidelines are broadly similar; both guidelines recommend performing spirometry and measuring FeNO to diagnose asthma and that clinical history-taking is an important part of the assessment.

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				We would therefore welcome efforts by all parties to work together present a single, comprehensive set of guidance for asthma to remove confusion for healthcare professionals and increase the likelihood that such guidance results in an improvement in care and outcomes for people with asthma.	NICE and BTS/SIGN are considering how best to clarify advice for those aspects of asthma care not covered by the NICE pathway for asthma diagnosis and management. NICE and BTS/SIGN are also discussing a longer term solution and how we might bring the two guidelines together.
Asthma UK	Short	18	8-10	The implementation section, 'Putting this guideline into practice', highlights these areas broadly as issues of effectiveness of use and availability for different objective tests (Short, p.18, lines 8-10). However, the implementation guidance does not offer specific advice for what are very likely to be common challenges for commissioners and practices implementing the guidance. A carefully considered and fully costed implementation plan will be key to ensuring the guidelines result in the desired improvement in clinical practice. It is critical that key stakeholders are involved in the development of this section before publication, including patient organisations such as Asthma UK, and other representative bodies such as PCRS-UK, RCP, RCGP and BTS.	. Thank you for your comment. This section is standard text and is included in all guidelines. The adoption team are developing an adoption resource to be published on the NICE website after guideline publication. The resource will be in line with the guideline and stakeholders will be contacted for comment.
Asthma UK	Full	49		**Recommendations for research** We welcome the following research recommendations that have been retained from the 2015 draft guidelines. *Diagnosing asthma in children and young people aged 5 to 16* What is the acceptability and diagnostic accuracy of objective tests that could be used to comprise a diagnostic pathway for asthma in children and young people aged 5 to 16 (for example, exercise challenge, direct bronchial challenge with histamine or methacholine, indirect bronchial challenge with mannitol and peripheral blood eosinophil count)? *Diagnosing asthma in adults (aged 17 and over)* What is the clinical and cost effectiveness of using an indirect bronchial challenge test with mannitol to diagnose asthma in adults (aged 17 and over)? Priorities for asthma research and development have been identified and published through the work of the European Asthma Research and Innovation Partnership (EARIP), a three-year collaboration between scientists, industry and people with asthma across Europe (see Masefield et al, 'The future of asthma research and development: a roadmap from EARIP', *Eur Respir J*. 2017 May 1;49(5)). Following a systematic review of the literature, experts noted the value of several biomarkers for their potential in asthma diagnosis. In addition to eosinophils, specific IgE and FeNO, the following biomarkers were highlighted and could be the basis for further research recommendations:	Thank you for your comment.

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				- Filaggrin mutations – In infants with eczema and food sensitization, genotyping of the FLG mutations allows the prediction of asthma before the onset of symptoms. - Th2 interleukins – Evidence suggests the role of Th2 interleukins as a biomarker, for instance IL-26 as a biomarker of disease severity in paediatric asthma without signs of Th2-mediated inflammation - Exhaled breath condensate – Studies have been limited but a difference has been found between the chemicals in the breath of severe asthma patients and healthy patients and may offer future hope. - Polygenic risk and genetic risk scores – Genetic risk assessments might be able to predict which childhood-onset asthma cases remit and which become life-course-persistent, who might develop impaired lung function, and the burden of asthma, although these predictions are not sufficiently sensitive or specific to support immediate clinical translation. It was felt that these biomarkers could be combined with improved indices on allergy and severity of wheezing episodes to predict future asthma in preschool children – a persistent gap in asthma diagnosis.	
Asthma UK	Full	194		The guidelines repeatedly state that 'a recommendation was developed' but there is no clarity on how this was developed (Full, p.96, 149, 194), no further detail on how these hubs might address the specific concerns raised by the GC, nor evidence that they are proven to do so. In the medium term, in the absence of diagnostic hubs, there is a considerable risk that the recommendations are viewed as irrelevant to the current structure of healthcare delivery, which could result in the guidelines being ignored. As above, there are risks to people with asthma in withholding any treatment until a diagnosis. Once hubs are active there could be implications as a result of delays in getting an appointment to undertake asthma diagnosis, and potential challenges in geographical access to the hubs. Leaving people with suspected asthma without treatment for this period is unsafe.	Thank you for your comment. The GC acknowledges that the recommendation on diagnostic hubs is not based on an evidence review. The GC believes the guideline is implementable and cost savings could be achieved through economies of scale if CCGs facilitate implementation. There is a recommendation to treat those who are unwell when they are first seen. Most people with new onset asthma are not acutely unwell when they present, hence the observation from several stakeholders that no wheeze will be present and spirometry will not show obstruction. The guidance does not preclude GP's from giving patients with suspected asthma a β-agonist inhaler to use if required whilst awaiting tests. We have also included advice about instructing patients to return if their symptoms worsen.
Asthma UK	Full	96, 149		Diagnostic Hubs	Thank you for your comment.

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				Diagnosis should be timely and accurate, while accounting for the fact that asthma is a variable condition, which can present problems for some diagnostic tests (i.e. spirometry). Beyond primary care, organisation of care is typically centred on either adults or children. A coordinated approach will be needed for asthma. This approach will need to reflect education, training and experience of the people working within hubs and communications to specialist teams. Considerable weight is placed on the role of diagnostic hubs to meet the 'concerns specific to spirometry' i.e. training to conduct spirometry (Full, p.96), and 'concerns specific to FeNO' i.e. the cost of the device and consumables (Full, p.149). This recommendation has links to the vision espoused in NHS England's Next Steps on the Five Year Forward View, which encourages practices to share diagnostic facilities and for STPs to demonstrate vertical integration to serve populations of 30,000-50,000 people.	
AstraZeneca UK Limited	Short	1	4	We note that the short guideline specifically calls out that this guideline is for healthcare professionals in tertiary care, amongst others. However, the final scope of the guideline states in section 4.3.2 that the tertiary care setting will not be covered by the guideline. Considering that severe, difficult to control asthma is likely to be diagnosed in tertiary care, and that this type of asthma is excluded from the scope of this guideline, we ask the GC to clarify the role of tertiary care in this guideline.	Thank you for your comment. The guideline is not about the diagnostic work that might be done in a tertiary care setting dealing with patients with difficult asthma. However, most tertiary care asthma physicians in the UK also act as the secondary care resource for their local population and the guideline will involve them in this regard. We agree that the current wording in the short guideline 'Who is it for?' section is ambiguous and have changed it.
AstraZeneca UK Limited	Short	13	4	We agree with the points listed about what action should be taken if asthma control is suboptimal. However, there will be cases where patients remain uncontrolled despite these changes made to their management. Therefore, to enhance this section, we suggest the addition of a recommendation to refer patients onwards if they remain uncontrolled, either to secondary or tertiary care. This will encourage uncontrolled patients to be managed in the most appropriate care setting. For example, patients with frequent OCS use may benefit from a referral. In addition, the BTS/SIGN 2016 asthma guidelines suggest referring any patients with features of acute severe or life-threatening asthma, as well as failure to respond to treatment, social circumstances or concomitant disease.	Thank you for your comment. Indications for referral was not part of the scope of this guideline.
AstraZeneca UK Limited	Full	17	7	Please note that the NICE technology appraisal for roflumilast (TA244) has recently been updated and published on 26/07/17. We therefore request the GC to update the guideline accordingly.	Thank you for your comment. The reference to NICE TA461 'Roflumilast for treating chronic obstructive pulmonary disease' has been updated in the full guideline.
AstraZeneca UK Limited	Short	22	3	We understand that the GC chose to exclude severe, difficult to control asthma from the scope several years ago. Since then, advances have been made in the monitoring and management of this type of asthma (for example with the recently updated 2017 NHS England service specification for severe asthma), with a significant change in the treatment options available for patients with severe asthma. Likewise, the GC for the asthma management guideline has excluded severe asthma management from scope. Due to recent advances and options available to severe asthma patients, and the understanding that many severe asthma patients take many years to reach a tertiary centre and receive an accurate diagnosis, we recommend that NICE issues guidance on the	Thank you for your comment. The decision to exclude severe asthma was taken during the scoping process (before recruitment of the GC) following consultation with stakeholders on what the guideline should and should not cover. The scope cannot be retrospectively changed. Your comment has been passed on to the Surveillance team at NICE for consideration when they review the need to update the timeline

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				management of severe asthma, as well as the diagnosis of severe asthma including the identification and referral of potential severe asthma cases. This will encourage equal opportunities for all types of asthma patients to receive the best care possible.	
Bedfont Scientific Limited	Full	149	9	We are concerned about the very subjective wording used with regard to the competency of the devices, the feasibility study appendice itself cites 'there is no formal assessment of competency for the use of the FeNO devices', however comments: "The project cited positive feedback for the NIOX VERO machine with very good patient compliance. All sites agreed that the device was easy to use and training was not lengthy (less than for spirometry). Moreover, fewer patients were unable to complete FeNO measurement than spirometry (5 vs 9). However it was noted that the NObreath device was difficult to use." Only 7 sites were recruited for the feasibility study and of these 2 sites used the NObreath, therefore these statements are based on a very, very small user base and without a formal assessment structure for feedback and therefore cannot be considered to be statistically reliable. The statements made here are also in direct conflict with the feedback supplied in the appendices from the feasibility study, namely: • Appendices A – R - page 851 - lines 2 – 5 - All sites received training from the manufacturer on use of the device and how to interpret results. There is no formal assessment of competency for the use of the FeNO devices, but this was reported to be straightforward by the sites and training took less than 1 hour. • Appendices A – R - page 852 - lines 8 – 9 - Six sites stated that FeNO was a welcome addition to the diagnostic process and an easy test to carry out, with positive feedback from patients. Moreover in April 2014 NICE published the 'Measuring fractional exhaled nitric oxide concentration in asthma: NIOX MINO, NIOX VERO and NObreath', which reviewed a plethora of clinical papers, user feedback and statistical data prepared by the diagnostics assessment committee, the School of Health and Related Research (ScHARR), and concluded that 'based on the available evidence, the 3 devices could, on balance, be considered to be broadly equivalent.' (section 6.2 of NICE Diagnostics Guidance 12). Bedfont also conduct post marketing surveillance regularly as part of our medical devices accreditation, we have not received this same feedback from our customer base, quite the contrary. Therefore to see this information presented in a very important document such as this is damaging to our reputation, our products' appeal and we feel does not fairly represent the products ease of	Thank you for your comment. The LETR has been amended to remove brand names of FeNO machines. The feasibility study reports the sites experiences but does not detail which device the comments were made about.

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				use again based on the 2 users surveyed compared to the hundreds of devices used worldwide. The NObreath has been available for sale since 2007 and has been used in a number of clinical studies in which have referenced the product as being easy to use (these can be provided upon request). In conclusion we feel the current wording used shows a biased view of the devices, which is in conflict with many other sources, including NICE Guidance specifically written to evaluate the device competency and therefore we respectively request that wording shown above in italics is removed from the final guidance.	
Bedfont Scientific Limited	Appen dix Q	851	Table 7	This table has omitted that the NIOX VERO has an operational lifetime of 5 years or 15,000 tests, whichever comes first and must be replaced with a new device at this point (Page 2 of NIOX VERO manual: http://www.niox.com/Global/NIOX%20VERO%20User%20Manuals/000191-09%20NIOX%20VERO_User%20Manual%20English.pdf). NObreath is unlimited by time or usage. This information should be added to the 'Other cost' column in Table 7.	Thank you for your comment. This table has been removed from the appendix and the information incorporated into the NICE Resource Impact Assessment where more detail about device costs, maintenance and need for replacements is presented.
Bedfont Scientific Limited	Appen dix Q	851	Table 7	The NIOX VERO test kits have an operational life of 'Maximum 12 months after opening package and installed in NIOX VERO® or expiration date as stated on the Sensor, whichever comes first' any unused tests at this time will be lost (Page 2 of NIOX VERO manual: http://www.niox.com/Global/NIOX%20VERO%20User%20Manuals/000191-09%20NIOX%20VERO_User%20Manual%20English.pdf). NObreath test kits are unlimited by time or usage. This information should be added to the 'Filters' column in Table 7.	Thank you for your comment. This table has been removed from the appendix and the information incorporated into the NICE Resource Impact Assessment where more detail about device costs, maintenance and need for replacements is presented.
Bosch Healthcare Solutions GmbH	full	gener al	gener al	Awareness will be the top challenging area to address: There are 12,000+ GP practices across the UK and raising the need for FeNO based on the guidelines will be a challenge. Most GP's will never have used FeNO or be aware of how to use it in practice (as the testing sites before). Many GP Practices will not have a GP or nurse that is not a respiratory focussed person either. Another challenge is the need for funding to successfully implement new diagnostic tools. Providing a FeNO measurement for all patients will have a significant positive impact on the overall therapy, but will also have a funding impact as there are either the cost of sending a patient to secondary care or buying a device for use in the practice. We believe the initial cost is not too much but any additional cost in present climate is a challenge if the money for FeNO testing has to be found at a local GP level. Funding support centrally either by NHS England/Scotland etc or funding via the local payers (Clinical Commissioning Groups and Health boards) would be a big advantage. A CCG could set up and fund FeNO testing at several localities in its area of responsibility where there is a focus on Asthma or respiratory. Alternatively working with Pharmacies to promote and provide FeNO testing could be a good solution as well.	Thank you for your comment. We agree with all the points you have made.
Bosch Healthcare	Short	5	7	Diagnostic hubs could be an answer to achieve economies of scale in the initial phase of guideline implementation but the availability for	Thank you for your comment. We agree.

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Solutions GmbH				patients should be the main focus: close to their residence as well as an appointment promptly after a suspected asthma diagnosis. And all diagnostic tests for asthma need to become part of basic training for general practitioner as well as for respiratory nurse practitioner. May groups of respiratory nurse specialists could become centres of excellence for assessment and advice and could lead the roll out of the guideline into the care practice. But financial incentives would be essential.	
Bosch Healthcare Solutions GmbH	short	14	4-9	1.5.4/1.5.5 Recommendation: Don't use FeNO routinely to monitor asthma control, only for patients who are symptomatic despite using ICS. Yes, FeNO measurement can help to identify ICS responder as well as adherence or inhaler issues, but furthermore recent studies have shown that FeNO measurement is a useful tool in monitoring and FeNO guided asthma management decreases the frequency of asthma exacerbations (Petsky et al. 2016, Murphy et al. 2016, Essat et al. 2016). But to profit from FeNO as a monitoring tool it has to be available for the responsible nurse practitioners and for dedicated patients for continuous monitoring and/ or self-management and not only at some specialised diagnostic hubs.	Thank you for your comment. The key word is "routinely". There may be circumstances in an individual patient where a FeNO measurement is useful outside this recommendation. We agree that FeNO would ideally be available in all GP practices. The recommendation about diagnostic hubs is given because many other stakeholders raised the issues of cost and training.
Bosch Healthcare Solutions GmbH		17		Algorithm C could mislead: The instructions on the left are not in the same order like the algorithm on the right. The algorithm should follow the order of recommended measurements with FeNO at the beginning.	Thank you for your comment. The instructions on the left suggest the order the tests should be done. The algorithm on the right shows how the results should be interpreted. Putting FeNO at the beginning would make the algorithm more complicated which was a criticism of the first draft guideline and that we have tried to address in this revised version.
Bosch Healthcare Solutions GmbH	Appendix Q	852	3-7	FeNO device issues collected from the feasibility testing sites: subjectivity in performing the test and interpreting the results should not occur, since there is a clinical practice guideline from the ATS for the interpretation of FeNO levels (Dweik et al. 2011). Display of a result despite incorrect measurement: depends on the chosen device, there are FeNO devices which show only results if the measurement procedure was conducted according to the ATS/ ERS recommendations for standardized procedures (ATS&ERS 2005, ERS technical standard: Horváth et al. 2017). And FeNO measurement results can be integrated into practice systems.	Thank you for your comment. The text documents the sites real world experiences. Two different devices were used by the sites. Thank you for signposting to the clinical practice guideline from the ATS for the interpretation of FeNO levels (Dweik et al. 2011). It would be beyond the scope of the clinical guideline, to include this reference however we will signpost to this from the adoption support resource which is being developed to support this guidance.
British Society for Allergy and Clinical Immunology	Short version	Whole document	general	In secondary care the burden of proof required may be different and this may need to be considered because patients often present after many years of poor response to asthma therapy	Thank you for your comment. The GC has developed a guideline that does not commit patients to a lifetime of medication without any objective indication of asthma. We agree that at present patients present to secondary care with a diagnosis of asthma but a poor response to treatment and that querying the original diagnosis is important in these cases. However, the potentially useful investigations in these cases will vary with the treatment currently taken, and this is beyond the scope of the guideline.
British Society for Allergy and Clinical Immunology	Short version	6	7-11	Reversibility testing should be either +ve BDR or PF variability or response to therapy and in conjunction with obstructive spirometry should be enough to make the diagnosis in all age groups - the guideline suggests that in adults two measures of reversibility are required This appears illogical and certainly impractical in General Practice	Thank you for your comment. In adults a single measure of reversibility in combination with evidence of airways inflammation diagnoses asthma. We agree that interpretation of some of the recommendations will be influenced by clinical experience, and also by the degree to which a test is positive or negative, since none of the tests have an absolutely definitive cut-off point. In a guideline it is necessary to specify a cut-off nonetheless. In the example you give we suggest measuring PEF variability after positive BDR only if FeNO is negative. This is a reasonable suggestion if the BDR is only just positive. If there is marked reversibility and the FeNO is borderline, we agree that asthma is the probable diagnosis.

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British Society for Allergy and Clinical Immunology	Short version	15	Algorithm2	The algorithms should be better laid out and ideally without repeating the decision boxes	Thank you for your comment. NICE will reproduce the algorithms in a separate document which will be formatted to be easily read when printed.
British Thoracic Society	General			The Society welcomed the pause introduced in the production of the NICE guideline to allow a pilot study of guideline implementation to take place in 2016. We note however that this draft guideline has been reissued for consultation with only minimal change from the previous consultation draft. It is not clear how the significant concerns about implementation which were reported from the pilot sites have resulted in any change in the guideline recommendations. The British Thoracic Society supports the response returned by the Primary Care Respiratory Society UK in outlining major concerns about the feasibility of implementation.	Thank you for your comment. The feasibility project demonstrated that the algorithms were implementable (appendix Q). Furthermore, there has been no new evidence published in the intervening period that would warrant a change in recommendations (appendix R). Therefore, the draft guideline has been reissued for consultation with changes in the presentation of the algorithms for clarity and simplicity, and additional recommendations around what to do with people at initial presentation and if access to bronchial challenge tests is limited. We address the comments from PCRS-UK separately.
British Thoracic Society				We are grateful that the full guideline provides an overview of asthma and acknowledges that there is no gold standard for the diagnosis of asthma. This creates a difficulty in evaluating tests as there is no standard reference against which to benchmark each test. We agree that the evaluation of the evidence is difficult and the assessed quality of studies in asthma is generally poor by the required standards set by NICE. As a result it will inevitably lead to conflicts when comparing practice and in adoption of new behaviours amongst clinicians. For such a prevalent disease with a large body of evidence, the publication base of studies considered at each section is relatively small and perhaps widening the scope of literature that could be used would help resolve some areas of uncertainty. We acknowledge that the guideline methodology adopted by NICE may be different to that used elsewhere by other organisations leading to differences in recommendations and this may cause increased confusion amongst the intended target audience. This could potentially be counterproductive if the guideline recommendations cannot be accepted because they are not concordant with current respected guidelines e.g BTS / SIGN Asthma guidelines and GINA. We acknowledge that since the previous draft a further evidence search has taken place that has found 9 further studies for consideration. We acknowledge and are grateful for a pause to allow a validation process to take place and that this is recognised and noted in the updated draft. We note that statements are included in each section. We note that the results of the feasibility testing in appendix Q show heterogeneity in numbers of asthma diagnoses with some resulting in fewer diagnoses, some increasing diagnosis and two showing no difference. Although this is a small sample it does	Thank you for your comment. We acknowledge your experience in this area and agree with you that the evidence base has limitations. However, we have used the highest grade of study that we could find for these diagnostic questions. The GC acknowledges that there are differences in the remits and methodologies used by both NICE and BTS/SIGN. For example, NICE uses GRADE methodology and considers cost-effectiveness evidence. Notwithstanding this, the GC considers the recommendations in both guidelines are broadly similar. The main difference between the BTS/SIGN guideline and NICE guideline is that the BTS/SIGN guideline permits no objective testing if the clinician is convinced of an asthma diagnosis on clinical history, whereas the NICE guideline recommends objective testing in all cases. NICE and BTS/SIGN are considering how best to clarify advice for those aspects of asthma care not covered by the NICE pathway for asthma diagnosis and management. NICE and BTS/SIGN are also discussing a longer term solution and how we might bring the two guidelines together. The accuracy of before-and-after comparisons in the implementation pilot is limited because the baseline data were not collected in real time. Bearing that limitation in mind, across the 5 sites that were able to estimate full baseline data, the number of people presenting with suspected asthma dropped from 190 to 100 in the baseline versus project period, but the percentage of asthma diagnoses increased from 11% to 20%, respectively. Across the 7 sites during the project period this proportion increased to 24.5% (35/143). Due to small numbers the data cannot be used to make conclusions about the incidence of misdiagnosis. However, all practices reported a higher level of confidence in the diagnosis of asthma during the project period. The project data may also reflect that GPs gave more thought to who they referred as 'suspected asthma' for diagnostic testing and assessment by the practice nurse.

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				highlight the fact that the guideline may not address one of the remits of the guideline which is to reduce the issue of misdiagnosis.	
British Thoracic Society	General			We appreciate the considerable effort that has been required for this document and commend the work of the NICE team. However the document is remains difficult to read in parts and we are unsure how practical a non-respiratory specialist (the intended audience) will find it. Some sections (e.g airway hyper-reactivity measures) are particularly dense and require repeated readings to take in every nuance of the algorithm, each slightly different to the next. We note that this may be a result of trying to quantify in objective tests that have relatively poor sensitivity / specificity, what a good physician does through good clinical judgement from experience, technical knowledge and discussions with the patient. A difficult task for the NICE team. The figures as visual representations are useful in conjunction with this.	Thank you for your comment NICE produces a short version of the guideline which only contains the recommendations. NICE recommendations are written in plain English. We have also produced algorithms which summarise the diagnostic pathway in visual form. The NICE Implementation team will also produce implementation tools to facilitate uptake of the guideline. We agree that clinical experience is hugely important, but would argue that this is most effective if allied to objective testing.
British Thoracic Society	Short	Table 1		Formatting error. Should there be something in the blank box for Children and young people such as "not suitable"?	Thank you for your comment. This change has been made.
British Thoracic Society	Short	Tables 2 and 3		It is not clear what to do if the outcome is "suspect asthma" as opposed to "diagnose asthma". We presume reassess after an interval or refer on for another opinion. Could this be made clearer from table 2 and 3? We think that the intention is to recommend a trial of treatment?	Thank you for your comment. We agree these tables should reflect the wording in the recommendation and algorithm and have made this change.
British Thoracic Society	Short	7	footnotes	Although it is an accepted and recognised diagnostic test with international guidelines on technique etc. It is confusing when producing a national recommendation that relies significantly on a bronchial responsiveness test which places responsibility on individuals for unlicensed use of medications that NICE has recommended. Would the individual be able to refer to the NICE guideline as a reason why they used the test if the patient came to harm even if suitable checks were made? Maybe an added section at the end would help.	Thank you for your comment. However, bronchial challenge is the single most accurate diagnostic test for asthma. The GC has tried to limit it to those patients who need it most. We assume that clinicians would refer to the NICE guideline as a reason why they used the bronchial challenge test'
British Thoracic Society	Short	7	Section 1.3.12	"Consider a direct bronchial challenge test with histamine or methacholine6 19 in adults (aged 17 and over) with: 20 obstructive spirometry and…." If the patient already has obstruction what is the advantage of a bronchial challenge test. If the FEV1 is less than 60% then it is not safe to perform challenge testing. This should be explained here. Also a positive bronchial challenge test in this situation does not diagnose asthma as patients with other conditions leading to obstruction would likely bronchoconstrict. Bronchiectasis, some bronchitic phenotypes of COPD etc Also if obstructed we would presume there would be an attempt at reversibility first. Other sections do cover this but not this one.	Thank you for your comment. We agree - in practice this would leave a very narrow window (between 60-70% FEV/VC ratio) and the challenge result in the face of pre-existing airflow obstruction is more likely to give a false positive result. We have therefore amended this recommendation and the corresponding part of the algorithm.
British Thoracic Society	Short	7	6	We are unclear of this line: "normal spirometry and the results of a FeNO test". Does this mean "normal spirometry and a normal FeNO" or "normal spirometry and a raised FeNO"? Should be made clearer.	Thank you for your comment. We agree and have amended the wording of this recommendation to clarify it's 'a positive or negative FeNO test'.

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British Thoracic Society	Full	15	38	This seems to give the wrong remit for the guideline!	Thank you for your comment. The original remit from NICE was to 'prepare a guideline on the diagnosis and **management** of asthma' – it was later decided at scoping to cover 'management' as the subject of a separate guideline as it would be too much to do in 1 guideline. A note has been added to the full guideline to clarify this.
British Thoracic Society	Full	40	3	We are pleased to see that considering occupational asthma is given high priority in the initial assessment of all cases of possible asthma as summarised in Algorithm A. We support the early referral of patients with work-related respiratory symptoms, as earlier investigations make the diagnosis easier, and early diagnosis improves prognosis. There is however an issue with the wording of the occupational asthma box. It currently says: "Check for suspected occupational asthma by asking employed people with newly diagnosed asthma, or established asthma that is poorly controlled: - are symptoms better on days away from work? - are symptoms better when on holiday?" At this point in the algorithm, patients haven't yet been diagnosed with asthma, and shouldn't be in the algorithm at all if they have established asthma. The occupational asthma box does however need to be in this first algorithm, to facilitate early referrals. It would be easy to solve this issue by changing the wording slightly to: "Check for suspected occupational asthma by asking employed people with wheeze, cough or breathlessness: - are symptoms better on days away from work? - are symptoms better when on holiday?" The advice to refer these people should remain - they should be presumed to have occupational asthma until a specialist proves otherwise, given this form of asthma is potentially curable.	Thank you for your comment. We agree that checking for occupational asthma is important and that it should be in Algorithm A, and also agree that the wording of the recommendation, although fine in itself, does not lend itself perfectly to insertion in the algorithm. NICE methodology does not allow use of different wording in an algorithm from that in the body of the guideline. We appreciate what you are trying to achieve with your suggested wording, but the GC wishes to retain wording which emphasises the importance of checking for occupational cause in both new asthma and in established asthma when control has become poorer.
British Thoracic Society	Full	43	25	It is recommended not to test for blood eosinophilia but this information may be available historically in the patient's contemporaneous notes as FBC is a common blood test that may have been done before. Should offer advice regarding this scenario?	Thank you for your comment. Blood eosinophil count was not shown to be an accurate test for asthma. Historical measurement might be of supporting value in a diagnosis but no more than that, and the value would in any case depend on the time elapsed and the circumstances in which the measurement was originally made.
British Thoracic Society	Full	44	25	Smoking may affect FeNO levels. There are other factors that can do this. Should this be stated also here?	Thank you for your comment. This is provided in the LETR for FeNO on page 147, first paragraph, of the full guideline.
British Thoracic Society	Full	45	21	The FeNO test is mentioned but not whether the result is high or low. This should be clarified.	Thank you for your comment. At this point in the diagnostic pathway the results of the FeNO test do not determine offering peak flow variability monitoring. The wording of the recommendation has been changed to make this clearer.
British Thoracic Society	Full	45	31	Often bronchial challenge tests would go up to 16 mg/ml and Pc20 between 8 and 16 would be regarded as equivocal with a suggestion to repeat the test if there is uncertainty.	Thank you for your comment. We agree that cut-off points for abnormal bronchial reactivity are not precise, and furthermore will vary with the challenge test protocol used. The GC decided against including advice about borderline results since this would complicate a pathway which was already being criticised for its complexity. Furthermore, in practice the advice on what to do with a borderline result would depend on the rest of the

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					evidence for asthma – how strong the history was, FeNO level etc. It is hard to capture all the possible nuances in a guideline.
British Thoracic Society	Full	87	13	NICE should comment on the ARTP recommendations which are endorsed by NHSE, and signed up to by BTS/SIGN, Asthma UK, BLF that all spirometry undertaken by 2021 needs to meet ARTP quality assured standards. http://www.respiratoryfutures.org.uk/knowledge-portal/education-for-health/improving-the-quality-of-diagnostic-spirometry-in-adults/	Thank you for your comment. The introduction of quality assured standards for spirometry is welcome, but this guideline is about the utility of the test result, not about how to perform the various tests.
British Thoracic Society	Full	146		The cutoff threshold for FeNO of 40ppb is queried. There is reference to a summary ROC curve that helped guide this decision. It may be useful to include this in the document as part of the evidence.	Thank you for your comment. The summary ROC curve can be found in Appendix J (sub-section 10.1.1; page 457).
British Thoracic Society	Full	149		There is reference to diagnostic hubs for centralising diagnostic testing for patients. This may be an option be there are no further details given as to the recommended size of these hubs, staffing costs and where they should be sited. Reference to existing hubs and how big they should be or how near to the patient population they should be sited should be included.	Thank you for your comment. The GC cannot provide this information, and it is likely that hub size and proximity to the patient will vary to some degree depending on local factors. .
British Thoracic Society	Full	153	Table 53	Why does the cost include two GP appointments when it does not feature elsewhere in the diagnostic test costing e.g. it does not feature for FeNO. This should either be removed for parity or be included in the other tests. We presume the GP will be seeing and assessing the patients for all the other tests so why only include it for interpreting blood tests?	Thank you for your comment. Eosinophils were not included in the economic model which is why the full cost was analysed separately. It was assumed all other tests could be conducted in the same appointment whereas blood tests require two appointments as the results need to be sent off and interpreted.
British Thoracic Society	Full	180	29	Understand on the evidence base NICE felt unable to comment on indirect BPT with mannitol however it is the only licensed test. Widely used in secondary care due to ease of use. The lack of comment needs review. Also we need to comment that a positive direct BPT with symptoms diagnoses asthma which is at odds with their comments on page 13 line 20-30.	Thank you for your comment. Based on the current available evidence the GC did not make a clinical recommendation for challenge testing with mannitol but made a research recommendation to guide future updates of the guideline. We agree that bronchial challenge tests are useful in diagnosis of asthma, hence the recommendation to use them when appropriate. Page 13 is part of the Introduction to the guideline and is intended simply to set the scene for the clinical questions which follow in the body of the guideline.
British Thoracic Society	Full	187	20.6	The evidence for all the exercise test studies in adult and paediatric patients are liable to significant bias yet no comment on under 17 testing approach.	Thank you for your comment. Exercise challenge test could be offered to under 17s based on the review of evidence, hence the wording of this recommendation; the evidence showed that this test was not clinically and cost effective in adults given the availability of better tests in this population group, therefore the GC made a 'Do not' recommendation in adults. But there was no evidence to suggest that it should not be done in children.
British Thoracic Society	Full	189		Regarding exercise testing for asthma. It is recognised that the prevalence of asthma amongst elite athletes may be higher than in the general population who also suffer from "asthma like" syndromes such as exercise induced laryngeal obstruction (see work of Hull et al). Although you have stated a lack of evidence for using exercise testing for diagnosing asthma in the general populace it would be worth stating that it may be useful in those who exercise regularly with symptoms or a recommendation for onward referral similar to recommendations for occupational disease.	Thank you for your comment. The role of specialist tests such as eucapnic voluntary hyperventilation to diagnose EIB in elite athletes is beyond the scope of these guidelines.
Circassia Limited	Short	4	14	Statement is misleading. Consider adding qualifying verbiage such as: FeNO should not be used routinely in patients who are well controlled, particularly if not taking ICSs.	Thank you for your comment. We believe that you mean page 14 line 4 rather than page 4 line 14. This recommendation is not intended only for those who are not using ICS, so your suggested amendment cannot be made. Other stakeholders have not questioned the meaning of the recommendation and the GC have not changed it.

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Circassia Limited	Short	5	14	FeNO should be recommended in patients taking ICSs that are symptomatic. See comments in full document below that cite newer data that provides evidence of effectiveness in these patients.	Thank you for your comment. A FeNO test is recommended for diagnosis in people with suspected asthma, and in monitoring for people with symptoms despite being on inhaled steroids; this latter recommendation is compatible with the published NICE DAP.
Circassia Limited	Short	5	15	Adult cut point of 40ppb should be reconsidered. See comments below for full document below.	Thank you for your comment. See response to your comment ID158.
Circassia Limited	Short	5	17	Why should children not get a FeNO first like adults? Study by Sivan excluded in error. See comments for full document below.	Thank you for your comment. The word "consider" in NICE recommendations reflects the strength of the evidence. In this case only one study of FeNO for diagnosis of asthma in children was included, whereas there were 5 for adults. Moreover, the large majority of children will get a FeNO measurement; only those with symptoms suggesting asthma and demonstrable reversibility of obstructive spirometry will by-pass FeNO. .
Circassia Limited	Short	5	23	Cut point for children of 35ppb should be reconsidered. See comments below in full document below.	Thank you for your comment. See response to very similar comment in ID158.
Circassia Limited	Full	92	20-23	This point raised regarding the ICS potential savings in children by enhanced opportunity for correct diagnosis and subsequent tailored appropriateness of ICS dosing, enabling cost prevention, contradicts the statement regarding significantly higher QALY for Children vs adults in management, which did not focus on ICS costs and needs to reflect the higher UK acquisition costs and frequency of use, of ICS in inhaler combinations compared to Europe.	Thank you for your comment. This cost savings refers to the costs borne by over-diagnosis. If a child does not have asthma but they are treated as such then the health service will bear unnecessary costs. Getting the diagnosis correct in the first place will prevent this.
Circassia Limited	Full	134	13	FeNO is not new. NIOX MINO first cleared for clinical use in the EU in 2004.	Thank you for your comment. The sentence reads "…FeNO is a **relatively** new diagnostic tool.." which the GC consider is a reasonable description of the current position of the test in the UK.
Circassia Limited	Full	134	25	Studies were missed in the review. Westerhof (ERJ 2015) and Wagener (Thorax 2015) both show FeNO can predict sputum eosinophils (gold standard for Th2 asthma). Karrasch (Thorax 2017) meta-analysis recommends FeNO, making broncho provoaction partially superfluous.	Thank you for your comment. All three studies were picked up by the search for the surveillance report and their full texts were assessed. Westerhof 2015 and Wagener 2015 do not fit the review protocol as they do not provide diagnostic accuracy data. The studies provide data on FeNO as a predictor for sputum eosinophils, but not on FeNO as a diagnostic tool for asthma. Karrasch 2017 is a systematic review. The included studies were checked for eligibility and relevant studies were included in the guideline.
Circassia Limited	Full	134	13,14	Diagnostic accuracy is not uncertain. Many studies have provided data comparing ability of FeNO to diagnose asthma either alone or in combination with other tests. As NHS states, FeNO is measure of airway inflammation and not obstruction, it should be viewed independently. New data provide evidence that demonstrates high level of prediction of airway inflammation. See newer studies cited below.	Thank you for your comment. This is the introduction to the section which explains why the GC wished to consider evidence around FeNO. Reading the numerous other comments from stakeholders in this document should make clear that in many clinicians' eyes the value of FeNO for diagnosis is uncertain, so the statement, in context of the introduction, is reasonable. However, we have amendedthe FeNO clinical introduction.
Circassia Limited	Full	135	2	The GC has excluded a study by Sivan et al with the argument that exhalation flow rate was not reported. However, the paper clearly states that the method conforms with published method guidelines (ref. no 12 and 16 in the paper). Both these guidelines clearly advocate an exhalation flow rate of 50 mL/s so this paper should have been included in the analysis	Thank you for your comment. We agree that the paper by Sivan et al could be included, although strictly speaking they do not state the flow rate (neither of their referenced papers mandate a flow rate). We have now added the Sivan paper to the guideline and removed it from the excluded study list.
Circassia Limited	Full	144	23	Sivan et al report a specificity of 89% at a cut-off of 25 ppb. Thus, again considering the existing literature, a cut-off of 25 ppb seems much more appropriate than the suggested 35 ppb in children aged 5-16 years. Most recent evidence to support this comes from Murray et al (Lancet Child Adolescent Health 2017).	The GC have explained the reason for choosing 35ppb in the full guideline. Whichever level was chosen, it would be possible to quote a single paper which suggests otherwise. The Murray paper is not published and we cannot comment on it.
Circassia Limited	Full	144	24	When using FeNO to support a diagnosis of asthma, the GC suggests a FeNO cut-off point of 40 ppb for adults and young people older than 16 years (25 ppb to rule out asthma in adults with obstructive spirometry), and 35 ppb for children aged 5-16 years. These cut-offs may be considered to be too high and they are not really supported by the literature, not even by the studies cited in the draft guidelines. Furthermore, the GC seems to have focused on the positive predictive value of FeNO, and thus neglecting the	Thank you for your comment. The GC acknowledge that there is an acceptable range of values that would constitute a positive FeNO test and there is no perfect cut-off. Other cut-offs were not shown to be cost-effective. The GC chose the diagnostic cut-off values for adults and children based on summary ROC curves which are provided in appendix J sub-section 10.1.1 on page 457. The diagnostic cut-off values recommended in this guideline are the same as those recommended by the BTS/SIGN guideline on asthma (page 18), (and the ATS suggest a higher level of 50ppb rather than the lower level you propose). Moreover, this guideline does not recommend using any single test to diagnose asthma, therefore a diagnosis of asthma will be supported by evidence from other objective tests and not on the basis of a FeNO test alone.

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				commonly reported high negative predictive values of FeNO, if the appropriate cut-offs have been chosen. FeNO is not a marker of asthma, but as GC states, it is a marker of Th2-driven inflammation in the bronchial mucosa. Thus, the cut-offs should be chosen according to the inflammatory signal and nothing else. See data from Westerhof (ERJ 2015) and Wagener (Thorax 2015).	
Circassia Limited	Full	144	16 (Table 49)	A FeNO test using the Niox Vero device can be performed with a single 10 sec test with results available on screen in one minute. On screen choice of tailored animations provide support for younger children to compete the test and it is licenced for use in children over the age of 4.	Thank you for your comment. The timing in this table includes time for getting the patient in and out of the room and explaining the procedure to them.
Circassia Limited	Full	145	22	Reconsider 40ppb (adults)/ 35ppb (children) as stated above	Thank you for your comment. Please see above our response to your previous comment ID158 which deals with the selection of the cut-off points.
Circassia Limited	Full	146	general	"FeNO test can be performed in around 10 minutes" is incorrect. Following a 10 second exhalation a FeNO result is provided by the NIOX VERO in approximate one minute: the exhalation test duration is either a 10 sec or 6 sec test (for children)	Thank you for your comment. You are ignoring the time required to get the patient in and out of the room and explain the procedure to them. We feel that 10 minutes is a reasonable time allocation for this test. By the time the machine has been turned on, warmed up, the patient has taken a couple of goes to get it right and then wait for 60 seconds for the result the average time is at least 5 minutes. The result then needs to be documented and, depending on the setting, discussed with the patient.
Circassia Limited	Full	220	12-14	Need for monitoring airway inflammation emphasised. Newer studies that demonstrate utility of monitoring FeNO vs blood and sputum eosinophils in improving asthma control have been recently published. See comments below.	Thank you for your comment.
Circassia Limited	Full	221	6	Several outcomes based studies comparing FeNO to conventional monitoring have been published that should be included: Petsky (Cochrane Meta Analyses: in adults September 2016, in children November 2016) Demonstrated significant effect of exacerbation reduction of >40% in over 3000 patients across 16 studies. Matsunaga (Allergerol International 2016) high FeNO levels related to loss of lung function Anderson (Annals Allergy Asthma Immunol 2016) Use of FeNO for dosing of ICS more accurate than FEV1 Cowan (JACI 2015) FeNO useful for ICS dosing Attanasi (Arch Med Sci 2016) Asthma control (ACT) correlates to FeNO Malinovschi (JACI 2016) Monitoring FeNO related to measures of asthma control	Thank you for your comment. The studies listed in your comment do not fit the inclusion criteria specified in the review protocol. The systematic reviews in adults and children (Petsky September 2016 and Petsky November 2016) were screened and their references were checked for eligible studies. Anderson 2016, Malinovsci 2016 and Matsunaga 2016 are observational studies and are therefore not eligible for inclusion in the review. Attanasi 2016 and Cowan 2015 do not fit the protocol criteria for intervention and comparisons and are therefore also not eligible for inclusion in the review.
Circassia Limited	Full	233	3	Study by Harnan included in this review yet was excluded in the FeNO diagnosis section (p. 144, line 4). Newer study by Sabatelli (J Invest Allergol Clin Imm 2017 demonstrated use of FeNO monitoring very cost effective)	Thank you for your comment. Harnan was excluded from the clinical evidence section, but we also do a review of health economic evidence which uses different criteria. The newer study you cite was published after our initial cut-off dates for exclusion in the guideline. After assessing the paper it was felt that it did not change the conclusions. The analysis has fundamental flaws, for example it does not state what utility values were used in the analysis. It is therefore unclear how a QALY value was derived. Secondly it is built on the same data used in the Harnan et al study, so although it is newer the evidence on which it is based is largely the same, only done in a Spanish context. Given Harnan is a UK study it would be deemed more appropriate evidence. A large part of what makes FeNO cost effective in both models is the assumption that the cost savings from ICS reduction will last for the rest of the individual's life. This is a strong assumption to make and in some cases ICS doses will increase. Therefore, regarding FeNO cost effectiveness, the same conclusions apply. It could be cost effective but the current basis of evidence has enough uncertainty to prevent a more universal recommendation being made.
Circassia Limited	Full	234	1	Cost analysis in children flawed by assumptions in study by Harnan. It is not plausible that the cost per QALY would be that different	Thank you for your comment. It is highly possible that cost per QALY differences could vary significantly between children and adults. The effectiveness of FeNO is different between both groups according to the

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				between adults and children. Analysis should be repeated with newer data from the Petsky Cochrane Meta analyses in adults and children.	evidence. The large difference in the cost per QALY comes from the fact that the evidence showed no change in ICS doses for children whereas a reduction in ICS doses for adults. In the Petsky study you cite it concludes "There were no significant differences between the groups for any of the secondary outcomes (forced expiratory volume in one second (FEV1), FeNO levels, symptom scores or inhaled corticosteroid doses at final visit).`so this evidence would not change the conclusions of their model.
Circassia Limited	Full	236	13 and 28	Studies that show no effect on rate of hospitalizations are usually underpowered to show a difference in children and adults. Elevated FeNO has been shown to be risk factor for future exacerbations across many studies (using a variety of definitions of exacerbations).See Kupczyk et al Clin Exp Allergy 2014.	Thank you for your comment. The evidence statements here are correct, and issues about power of the studies were taken into account by the GC when considering this evidence.
Circassia Limited	Full	236	43	Should be restated. FeNO monitoring in well controlled patients not taking ICS is not recommended	Thank you for your comment. The committee do not agree that your change to the wording is appropriate. Routine monitoring should only be applied to well-controlled asthma (poorly controlled asthma requires more active management) so the added words are redundant.
Circassia Limited	Full	237	44	FeNO monitoring should not be optional particularly in patients who are at risk for exacerbations and have trouble with asthma control. In addition, patients taking high dose ICSs are at risk for adverse effects and should be periodically re-evaluated to assess potential for reducing ICS doses. Without FeNO how do physicians optimize ICS doses? Using FEV1 is not a sensitive marker of airway inflammation and thus not useful to measure effect of anti-inflammatory treatment with ICS.	Thank you for your comment. The GC reviewed the currently available literature as described in the LETR which includes the line you refer to. This LETR explains in some detail why the GDG arrived at their recommendations.
Circassia Limited	Full	240	General	FeNO is useful as a tool to determine adherence to ICS. Studies that have investigated this are typically real world observational analyses since RCT study design constraints will negative results.	Thank you for your comment. However, the GC based their recommendations on the highest level of evidence available. .
Circassia Limited	Appendix	851	8-11	Define which device this comment was linked to (NOBreath or NIOX)	Thank you for your comment. The feasibility project was not designed to assess individual devices and reference to specific devices will not be included.
Circassia Limited	Appendix	851	6	Define which device this comment was linked to (NOBreath or NIOX)	Thank you for your comment. The feasibility project was not designed to assess individual devices and reference to specific devices will not be included.
Circassia Limited	Appendix	851	(Table 7)	Prices related to NIOX Vero are incorrect. Correct prices related to NIOX Vero as follows: Niox Vero instrument /device costs, should be. £2640 excluding VAT (this includes delivery, set up and training); Software costs are free of charge in UK and included with instrument purchase; 100 test sensor is £8.30 per test, 300 test sensor is £5.03 per test, 500 test sensor is £4.58 per test, 1000 test sensor is £4.84 per test (reference Circassia UK pricing 2017)	Thank you for your comment. The prices displayed were provided by the companies to the sites when the project started in April 2016. As these will not be accurate at time of guideline publication the table has been removed from Appendix Q and the information incorporated into the NICE Resource Impact Assessment.
Cornbrook Medical Practice				Thank you very much for improving the guidelines, after the feasibility project. We feel that changes recommended have been listened to and now form part of the guideline.	Thank you for your comment.
Cornbrook Medical Practice	Short	6	19	Is a bit confusing, should we say normal spirometry, and positive or negative FeNO	Thank you for your comment. We agree and have amended the wording of this recommendation.
Cornbrook Medical Practice	Short	6	22	Would be useful to define, how peak flow variability is calculated	Thank you for your comment. The optimum way of calculating PEF variability is to express the difference between highest and lowest values as a percentage of the mean of all measurements. In practice this requires entering the values into a calculator or computer, and in most instances it is perfectly acceptable to calculate the difference between highest and lowest as a percentage of the highest value.
Cornbrook Medical Practice	Short	7	6	Is a bit confusing, should we say normal spirometry, and positive or negative FeNO	Thank you for your comment. We agree and have amended the wording of this recommendation.

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Cornbrook Medical Practice	Short	15	Whole page	Not very clear to the eyes, difficult to read, agree with content, its just how the display is	Thank you for your comment. NICE will reproduce the algorithms in a separate document which will be formatted to be easily read when printed.
Cornbrook Medical Practice	Short	16	Whole page	Not very clear to the eyes, difficult to read, agree with content, its just how the display is	Thank you for your comment. NICE will reproduce the algorithms in a separate document which will be formatted to be easily read when printed.
Cornbrook Medical Practice	Short	17	Whole page	Not very clear to the eyes, difficult to read, agree with content, its just how the display is	Thank you for your comment. NICE will reproduce the algorithms in a separate document which will be formatted to be easily read when printed.
Danone Nutricia				I have reviewed the draft guideline and we don't have any comments to add.	Thank you for your comment.
Department of Health				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 consultation.	Thank you for your comment.
Education for Health	Full	general		We welcome the recognition of diagnostic difficulty in asthma and the efforts to improve accuracy in the diagnosis of asthma and the recommendations for the use of a range of objective tests. We are concerned that many of the recommendations are beyond the current scope of primary care. We are concerned that the recommendations are not in line with current British asthma guidelines which are widely accepted and used in health care. We feel that strong recommendations around the education and training of HCPs must accompany this guideline to support implementation We are disappointed that the principle of "probability", although alluded to is not specified. In general the algorithms and tables are complicated and may be difficult to understand, potentially leading to errors in diagnosis	Thank you for your comment. We agree that the guideline recommends doing more tests and some changes in primary care organisation and training will be needed to facilitate this. The GC acknowledges that there are differences in the remits and methodologies used by NICE and BTS/SIGN and this has resulted in some differences in the guidance offered. Although we agree that the BTS/SIGN guideline is widely used in the UK, we do not think that its diagnostic recommendations are implemented as widely as its treatment recommendations. We agree that training for healthcare professionals will be needed to support implementation. However, recommendations on service delivery are outside the remit of this clinical guideline. Regarding your point about probability, the BTS/SIGN guideline on asthma tries to build an algorithm around probability following history-taking but this has not been adopted as part of routine clinical practice.
Education for Health	Full	108-116	General	Peak flow monitoring for the diagnosis of asthma is extensively used in primary care, it is simple, non-invasive, widely available and inexpensive with a high specificity to provide objective evidence of variable airflow obstruction. Whilst it remains in the proposed guidelines it is advocated for clarification in cases of clinical uncertainty following more expensive and less easily available tests thereby creating a gap in current practice. Arguably the test does rely on patient technique, effort and concordance but the same principles also apply to the more expensive and less available tests. We feel that peak flow monitoring is more likely to be complied with if introduced early at an initial presentation when the patient is symptomatic and can be a powerful patient education tool with visual results demonstrating response to treatments.	Thank you for your comment. The GC did not consider that PEF variability showed sufficient diagnostic accuracy to warrant recommending it first-line. We agree that it can be a useful tool once treatment is started, as an aid to demonstrating the degree of improvement. We disagree that the guideline has a lack of emphasis on good history-taking; clinical history-taking is the vital first part of the assessment. It is true that more pages of the guideline deal with tests rather than symptoms, but there is less evidence around symptoms, and fewer to consider compared to potential tests.

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				The diagnostic algorithm proposed in the new guidelines dictates a greater reliance on less available and more costly investigations and referral to secondary care services resulting in delayed diagnosis and treatment for individual patients alongside additional pressures lengthening secondary care referral times. There is a lack of emphasis on good history taking which involves asking about previous respiratory illnesses, treatments and response to treatments – including treatments given in the past for wheezing.	
Education for Health	Full	54-57	General	The overall quality of evidence on which recommendations for significant changes to practice is low and there is little consideration of real world data. It is of concern that there is limited evidence for children and no evidence underpinning recommendations for diagnosis in 5-16 year olds	Thank you for your comment. Adding observational series or case studies is unlikely to raise the quality of the evidence. You do not say which data you propose that we include. Regarding your second point, see response to identical comment in ID122.
Education for Health	Full	89-91	All evidence tables	All evidence for the recommendation is outside the 10-year recommendation of 'valid evidence' and involves small numbers. The evidence for children is non-existent and not appropriate in all areas. NICE acknowledges this but continue to make recommendations with no evidence base.	Thank you for your comment. Age in itself does not invalidate evidence. We agree that better evidence would be useful, but even if no evidence whatsoever had been found (not the case) it is appropriate for the GC to try to formulate recommendations if they can do so by consensus.
Education for Health	Full	43	20	We agree that patients presenting acutely unwell must be managed in accordance with their presentation however the recommendation appears to contradict the foundation for diagnosis that NICE are proposing i.e. diagnosis is not made on the basis of a single objective test. Given the variable nature of asthma it would be helpful if NICE could clarify this point and offer guidance to primary care practitioners about how to proceed with diagnosis in this situation.	Thank you for your comment. The GC has developed recommendations and algorithms that aim to treat people who are acutely unwell, but if possible not commit them to a lifetime of medication without any objective indication of asthma. In the minority who present with an acute attack the guideline suggests performing objective tests later. It is true that circumstances might dictate that the diagnosis then has to made on the basis of a single test if, for example, the patient was so unwell at presentation that the practitioner does not feel able to suggest a temporary withdrawal of inhaled steroids, so we have removed the recommendation on not diagnosing on the basis of a single result.
Education for Health	Full	44	General	We are concerned that FENO is poorly understood by health care providers and the normal range varies. It is not acceptable for NICE to state regard readings greater then 40ppb as a positive test as this is misleading and could lead to errors in diagnosis Q1 there are significant implications relating to the training and education of HCPs that we feel NICE fails to address	Thank you for your comment. The GC acknowledge that there no perfect sharp cut-off point for FeNO, but this applies to many tests used in medicine yet they still have value if used in clinical context. The GC chose the diagnostic cut-off values for adults and children based on summary ROC curves which are provided in appendix J sub-section 10.1.1 on page 457. The diagnostic cut-off values recommended in this guideline are the same as those recommended by the BTS/SIGN guideline on asthma (page 18). There are no new data that suggest different cut-off values should be used to indicate a positive test. Moreover, this guideline does not recommend using any single test to diagnose asthma, therefore a diagnosis of asthma will be supported by evidence from other objective tests and not on the basis of a FeNO test alone.
Education for Health	Full	44	5	Q1 This recommendation will be challenging in practice because in general most 5 year olds cannot perform objective tests Q3 Guidance to CCGs about commissioning and access arrangements for paediatric diagnostics as this usually falls into the specialist commissioning area	Thank you for your comment. We agree that performing tests in this age group can be more challenging than in adults, but this is true of tests for other conditions, not just asthma; it doesn't mean the tests should not be done. The GC has made specific recommendations in children and young people around what to do if they cannot perform the tests at that point in time. The GC cannot give specific advice about arrangements for paediatric diagnostics as this will vary depending on existing facilities, but diagnostic hubs for paediatrics might also be appropriate.
Education for Health	Full	44	15	Too vague, clarity needed for smoking and other factors affecting FENO levels	Thank you for your comment. The GC is not aware of any definitive data on which to measure precisely how FeNO levels are affected by smoking since this may vary with amount smoked and time since last cigarette. The GC do not consider that smoking is a significant enough reason not to do a FeNO test, because the presence of smoking reduces rather than removes the signal, the prevalence of smoking in the general population is around 20% (and is similar in people with asthma); therefore the majority of people attending a FENO test with suspected asthma are not affected.
Education for Health	Full	44	17	Q1 and Q1 FENO is not used in primary care and it remains cost prohibitive	Thank you for your comment. See above response to very similar comment (ID99).

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Education for Health	Full	44	30	Does not reflect LLN for children	Thank you for your comment. Please see the footnote. We have now changed this recommendation.
Education for Health	Full	45	4 - general	We are concerned that NICE is further complicating what is already complex. Further clarification is required to explain why, in a patient with a clinical history suggestive of asthma with a positive BDR, further objective testing is required	Thank you for your comment. The GC acknowledges that diagnosis of a complex variable disease can be challenging. To answer your specific example, bronchodilator reversibility has a false positive rate and the diagnosis of asthma is more secure if FeNO is also elevated.
Education for Health	Full	45	1	Why is this "consider" not offer, if a child can perform spirometry and it is obstructive (based on age appropriate LLN) why would you not recommend BDR	Thank you for your comment. The wording of the recommendation is based on the strength of the evidence regarding the diagnostic accuracy of the test, and not the child's ability to perform it.
Education for Health	Full	46	General	We welcome the recognition of PEF variability as a valuable tool in the diagnosis of asthma. We are concerned about the level of emphasis placed upon the role of FENO in diagnosis. This guideline seems to biased toward a test that is poorly understood, expensive and is largely inaccessible	Thank you for your comment. The review of evidence on the diagnostic accuracy of FeNO showed it to be better than PEF variability and in particular to be a much more sensitive test.
Education for Health	Full	46	9	We are concerned that these tests are not available in primary care and not readily available in secondary care and therefore will be difficult to implement.	Thank you for your comment. Spirometry, bronchodilator reversibility and peak flow variability monitoring are currently available in primary care. FeNO measurement is not currently widely available, but the review of evidence has shown it is a useful test in the diagnosis of asthma, so it would be wrong not to recommend it in this guideline. We hope this will lead to increased service provision. We also agree that bronchial reactivity is not widely available in secondary care, but this is the single most accurate objective test for asthma and it therefore needs to be included for use when the rest of the patient assessment has been equivocal.
Education for Health	Full	47	General	Q1 and Q2 there are implications relating to both the implementation and costs of the recommendations to refer patients for specialist opinion if they have symptoms suggestive of asthma with a positive objective marker such a BDR. This seems an unnecessary step.	Thank you for your comment. The recommendation to refer for specialist opinion is only made if there is diagnostic uncertainty on completion of the algorithm. We would expect this to already be occurring as part of routine clinical practice.
Education for Health	Full	47	Table 7	Helpful presentation but does not accurately reflect LLN for obstruction in children – this needs to be much more clear otherwise there will be greater risk of error	Thank you for your comment. See response to very similar comment in ID119.
Education for Health	Full	68	27	We support the recommendation however feel it could be better related to and more effectively support clinical practice by clearly linking the questions to probability values	Thank you for your comment. The review of evidence showed that a personal or family history of atopic disorders alone is not enough to base a diagnosis of asthma on, but is an important question to ask in clinical history-taking.
Education for Health	Full	75	12	We support the recommendation	Thank you for your comment.
Education for Health	Full	78	19	Although we acknowledge that no evidence met the search criteria, it is disappointing that there is no recommendation from NICE about consideration of symptoms related to taking certain drugs in the diagnosis of asthma. It is currently standard practice, and an important educational point, for HCPs to ask if symptoms occur in response to .. anything, given the heterogeneous nature of the condition.	Thank you for your comment. Please see the LETR on page 79 'other considerations' for the GC's rationale for making no clinical recommendation given the absence of evidence: "*The GC suggested that the lack of evidence derives from the fact that taking a clinical history of symptoms after using medication is not routinely used in the diagnosis of asthma; rather, it is used to characterise a particular asthma phenotype in order to guide management, e.g. for the avoidance of certain drugs. The GC stated that around 1 in 12 people with severe asthma have a response to drugs and further research may be beneficial to determine the diagnostic test accuracy of taking a clinical history of symptoms after using medication. Anecdotally, clinicians may find a history of respiratory symptoms in response to specific drug exposure useful in increasing the suspicion of a diagnosis of asthma; however, mandating to ask or not ask the question is not possible based on current evidence*."
Education for Health	Full	85	1	We are pleased to see that this recommendation mirrors BTS/SIGN guidance and that the education of HCPs can continue to focus on the identification of people who may have occupational asthma	Thank you for your comment.

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Education for Health	Full	87	General	The introduction to the spirometry section does not recognise that flow volume loops are not commonly performed in primary care. It also fails to acknowledge of the role of FEV1/VC to diagnose obstruction if that volume is higher.	Thank you for your comment. This is simply an introduction to a section the primary purpose of which is to consider whether spirometry has a role in asthma diagnosis. We agree that it omits many facts about spirometry, but it is not supposed to be an exhaustive description of the test.
Education for Health	Full	92	Table 28	The table for the cost of spirometry does not take into account training. It also only accounts for a 10-15 minute appointment (appt) which is a pre bronchodilator appt, There is then the administration of the drug (not costed and sometimes nebulisers are used – also not costed but recommended in guidelines) and then there is a repeat 10-15 minute appt. Therefore, this costing is inaccurate.	Thank you for your comment. The training cost is not included as this would be marginal on a cost per patient basis. As the newly trained clinician tests more patients, the per-patient cost of training falls. Likewise it was felt a lot of centres would already have this training in place as spirometry is vital in the COPD diagnostic pathway, therefore it would not represent an incremental cost. This table outlines the cost for just a spirometry, the additional drug cost you refer to is used for testing bronchodilator reversibility, which is cost in table 32.
Education for Health	Full	94	Last two paragraphs	Whilst we recognise the potential value of FENO the time needed for the inclusion of this in appts with spirometry has not been costed. The amalgamation of several clinical tests is noted to be the most cost effective strategy - where are the total costings to include nurse training and equipment costs which are prohibitive to primary care (as outlined by the feasibility studies). Within the feasibility studies those that said they would continue with FENO said it was because they had free equipment.	Thank you for your comment. The additional time taken to conduct FeNO alongside spirometry has been included in the economic model. Two separate analyses were also conducted whereby a separate appointment is required for FeNO (see sensitivity analysis 17 in the model write-up) and FeNO remained cost effective. The adoption team are planning to develop a web based document which shares learning from the sites involved in the feasibility study to support those in practice responsible for implementing this guideline. The sites who would continue with the algorithm said this was helped by getting the FeNO equipment, which is not quite the same thing as continuing because they received it. Nonetheless, we agree that take-up of FeNO would probably be much increased if it were possible to be given the equipment for nothing
Education for Health	Full	95	First paragraph	The definition of a positive test is not present as is the lack of evidence. The studies that are utilised are weak with a low to moderate grade criteria.	Thank you for your comment. The definition of a positive spirometry test is given in the recommendation: "Offer spirometry to adults, young people and children aged 5 and over. Regard a forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ratio of less than 70% (or below the lower limit of normal if this value is available) as a positive test for obstructive airway disease (obstructive spirometry)." We agree that the evidence base is weak but these are the best available studies on this topic. We agree that spirometry is not the most sensitive test for asthma, hence a diagnosis of asthma should not be made on the basis of a spirometry test alone. And since the presence of bronchodilator reversibility is a hallmark of asthma, the GC consider spirometry is a useful test and it would be wrong to omit it. It is a key test in the BTS/SIGN guideline so it is not a change in practice.
Education for Health	Full	95	Last paragraph	The compromise between scientific accuracy and usability has been acknowledged by GC but interesting the expert group chose to use LLN when the respiratory community do not agree this and the evidence variable.	Thank you for your comment. . The criticism we have received has generally been for not using LLN, and we have now changed this.
Education for Health	Full	98	23	FEV1 reversibility has no evidence base.	Thank you for your comment. We are not completely sure what you mean, but think you are saying that there is no reference on the statement about ATS/ERS taskforce – if so, thank you, reference inserted.
Education for Health	Full	99	10	No evidence for children	Thank you for your comment. Regrettably there is generally less evidence to inform the recommendations for children, and therefore the GC have made a weaker 'consider' recommendation in children and young people.
Education for Health	Full	103	Table 32	Need first pre test to be included in costs	Thank you for your comment. The pre-test cost was included in the economic model as bronchodilator reversibility was assumed to follow straight after the first spirometry was conducted.
Education for Health	Full	104	Last paragraph	The guidance recommended is not NICE 2010 of 400mls (not sure why not using NICE guidance to underpin another NICE guideline.)	Thank you for your comment. We believe this refers to the 2010 COPD guideline. The recommendations within that guideline which mention 400mls as indicative of asthma were both consensus recommendations. They are couched in terms of a degree of reversibility which effectively excludes COPD, whereas our recommendation on reversibility is based on setting the most accurate cut-off point for asthma diagnosis (irrespective of whether COPD is considered the most likely alternative). Moreover, the question of reversibility was not part of the 2010 COPD update, so the recommendations were actually derived for the 2004 guideline. The evidence search for that guideline was based on COPD populations, and the GC were concerned about distinguishing COPD from asthma. Our recommendations are therefore based on a different and more up to date evidence search.

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Education for Health	Full	106	Last paragraph	The paragraph above acknowledges there is no evidence or poor quality evidence but the statement then says that 'there was sufficient evidence to make the statement?'	Thank you for your comment. We have amended the first line of the 'other considerations' section to read "The GC agreed that there was sufficient evidence to make a recommendation **in adults**".
Education for Health	Full	130	38	We support this recommendation	Thank you for your comment.
Education for Health	Full	134	13/14	We welcome the recognition of diagnostic uncertainty with FENO and therefore fail to understand why this draft guideline emphasises its role so heavily	Thank you for your comment. You quote a sentence from the clinical introduction to the FeNO section which simply explains why the GC needed to look at the evidence. The point the FeNO clinical introduction is making is that FeNO is a relatively new test and therefore its utility in the diagnosis of asthma warrants a review of the evidence. Following the review of evidence it was found to be a useful test. The FeNO clinical introduction has been changed to clarify this.
Education for Health	Full	144	General	The economic evidence for FENO is not clear and transparent as the cost breakdown does not appear to be complete	Thank you for your comment. The section you refer to is but a small part of the overall analysis which can be found in the full model write-up in appendix M.
Education for Health	Full	190	7	We support the recommendation about the development of diagnostic hubs	Thank you for your comment.
GP update / Red Whale	General			I feel that NICE has lost it's way in this guideline and common sense seems to have been abandoned. This guidance needs to set out clearly what advantages spirometry+FeNO has over spirometry alone (the diagnostic test UK primary care are currently using based on the BTS/SIGN guidance). Then it needs to explain the evidence for adding up to 3 further tests. The questions I can not find the answer to are: • Where is the evidence that FeNO+spirometry for everyone is better than spirometry alone (reduction in mortality/morbidity)? • Where is the evidence that adding PEFR variability testing (on top of FENO+spirometry) to certain groups improves patient care (reduced mortality/morbidity)? • How many over-diagnoses are prevented with the proposed pathway? And are any of these over-diagnosed patients coming to harm as a result of over-diagnosis under the current pathway? • How many people are currently under-diagnosed **and harmed by this** and would therefore benefit from this more complex testing regimen? • How many people will be lost to follow up because of the complexity of needing sequential tests? Might they come to harm as a result? • What proportion of people presenting to primary care with the key symptoms (wheeze, cough, breathlessness) will end up going down each arm of pathway? This matters because if most people need 3 or 4 tests this is a huge increase in workload – if however the majority of people are diagnosed based on FeNO and spirometry, this may be more manageable. Without evidence of clear patient benefit and clinical outcomes I can not see primary care welcoming or adopting such complex guidance.	Thank you for your comment. You are effectively asking for evidence that the diagnostic pathway as a whole is effective in terms of outcomes of morbidity/mortality/diagnostic accuracy. No guideline can ever give this evidence at the time of production; each recommendation is based on best available evidence, but the effect of linking them all in the guideline will not be apparent until implemented. NICE guidelines on other conditions are published without initial testing, and the same applies to other guideline developers. This guideline on asthma has gone a step further and piloted the algorithms for 6 months and demonstrated that they are implementable. We also note that the health economic analysis, which synthesises all the relevant study outcomes, shows the proposed pathway to be cost-effective. Most of your bullet-pointed questions cannot be answered on current evidence. There is no morbidity/mortality data addressing the role of adding FeNO to spirometry, nor the role of adding PEF variability to both. The question on prevention of over diagnosis would require a study in which conventional diagnosis practice is compared to the proposed NICE pathway. However, as a general principle it is surely desirable to reduce over and under-diagnosis as far as is possible, since the correct diagnosis is being missed in both cases and the patient is not receiving the correct treatment. Regarding loss to follow up, in the feasibility study 20% of the patients who got to the point of needing PEF monitoring did not complete the measurements. However, it is our experience that a proportion of people fail to complete a PEF diary if it is the first thing they are asked to do. Regarding the increase in number of tests required, in the feasibility study 14 out of 143 reached the point at which bronchial challenge would be required. The majority therefore need 2 or 3 tests. Note however, that FeNO and spirometry can be done at the same visit. We do agree that there will be an increase in workload, but not a huge increase, and this is particularly true if the current BTS/SIGN guidance on diagnosis is being followed correctly since that requires at least 2 visits even in those deemed to have high probability of asthma on first clinical assessment.

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GP update / Red Whale	Full version	142-143	3	From what I can see in table 48, the diagnostic accuracy for FeNO testing in adults is based on 5 trials (821 people) all of which were assessed as moderate to very low quality. Is that sufficient evidence to change national diagnostic pathways, with the associated cost implications?	Thank you for your comment. The derivation of the GRADE rating is such that most outcomes tend to be rated Low or Very Low. A single GRADE quality rating is assigned to the whole body of evidence available for each outcome of interest and, for example, even if some of the studies were excellent quality, between-study heterogeneity can lower the quality assessment. We assume that by "current national diagnostic pathways" you mean the BTS/SIGN guideline. As cited in the guideline, current practice leads to a significant level of misdiagnosis.
GP update / Red Whale	Full version	42	1	The algorithm for adults (which summarises the guidance): The guidance suggests all adults will need 2 tests (FeNO and spirometry) and some will need 3 or 4 tests (FeNO, spirometry, peak flow variability, hypersensitivity testing). For each test the guidelines summarises the evidence for each test (based on relatively small numbers, with the gold standard often being a physician assessment and a test of some sort!) however I could not find any evidence that SEQUENTIAL testing (i.e. doing spirometry, followed by FeNO, followed by PEFR variability, followed by hypersensitivity testing) increased the chance of getting the diagnosis right. Where is this evidence? I could not find any evidence in the guidelines that the NICE approach is any better than the rather more pragmatic British Thoracic Society/Scottish Intercollegiate Guidance which could be paraphrased as "If the history sounds like asthma, treat it as asthma, and see how the person responds, based on lung function or validated symptom score." Where is this evidence? Have you considered what the loss to follow is if patients are tested for FeNO and spirometry and then sent away to do serial peak flow readings for 2-4 week? (and if spirometry is done in the practice and FeNO is the hubs the guidance suggests, what will the loss to follow up be then?). Is there a clinical safety issue here – could patients suffer from an asthma attack whilst they are waiting to jump through all the hurdles of the diagnostic tests?	Thank you for your comment. As in your previous point, you are effectively asking for evidence that the diagnostic pathway as a whole is effective in terms of outcomes of morbidity/mortality/diagnostic accuracy. No guideline can ever give this evidence at the time of production; each recommendation is based on best available evidence, but the effect of linking them all in the guideline will not be apparent until implemented. NICE guidelines on other conditions are published without initial testing, and the same applies to other guideline developers. This guideline on asthma has gone a step further and piloted the algorithms for 6 months and demonstrated that they are implementable. We also note that the health-economic analysis, which synthesises all the relevant study outcomes, shows the proposed pathway to be cost-effective. We would paraphrase the BTS/SIGN guideline slightly differently "If the history sounds convincingly like asthma, treat it as asthma, and see how the person responds, based on lung function or validated symptom score.". You have assumed that all patients fit in the high probability group of the BTS/SIGN guidance; if that guideline was followed accurately many patients would be judged as intermediate probability and get objective tests. Even in the high probability group there are two visits since it is incumbent to see how the patient responds to treatment and to assess this with lung function or a validated symptom score – and of course, this means that that measurement has to be made at baseline. The number of "hurdles" to jump is in fact comparable in both guidelines if BTS/SIGN is applied properly.
GP update / Red Whale	Full version	43	17-20	This is unclear and open to misinterpretation. The statements about if being unwell and doing diagnostic tests are unclear. I think you mean: Do diagnostic tests at presentation, unless the person is unwell (although this will not be possible if people need referring to a hub!). If unwell, treat. Once well do diagnostic tests.	Thank you for your comment. We have changed the wording of the recommendation: 1.1.5 Treat people immediately if they are acutely unwell at presentation. If the equipment is available and testing will not compromise treatment of the acute episode,possible, perform objective tests (including fractional exhaled nitric oxide [FeNO], spirometry and peak flow variability) at the time of presentation. If objective tests cannot be done immediately, they should be done when acute symptoms have been controlled, but advise patients to contact the practice immediately if they become unwell while waiting to have objective tests.
GP update / Red Whale	Full version	44	25	Unhelpful. What does this mean to me as a practicing GP? Please give reference ranges for smokers. If they don't exist why not???	Thank you for your comment. The GC is not aware of any definitive data on which to measure precisely how FeNO levels are affected by smoking since this may vary with amount smoked and time since last cigarette. The GC do not consider that smoking is a significant enough reason to not do a FeNO test, because the presence of smoking reduces rather than removes the signal, and we have added to the recommendation to emphasise this. Of note, the prevalence of smoking in the general population is around 20% (and is similar in people with asthma); therefore the majority of people attending a FENO test with suspected asthma are not affected. The recommendation now reads:

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					1.3.4 Be aware that a person's current smoking status can lower FeNO levels both acutely and cumulatively. However, a high level remains useful in supporting a diagnosis of asthma.
GP update / Red Whale	Full version	45	26	Are theses tests that can be done in primary care or do they require full resuscitation facilities? What is the mortality rate from such tests?	Thank you for your comment. At the moment bronchial challenge tests with histamine or methacholine are only available in secondary care.
GP update / Red Whale	Full version	145	18-21	Do the proposed complex diagnostic pathways hang purely on economic modelling? Has NICE considered how people presenting to primary care may be less well selected than those enrolled in clinical trials and therefore the number of tests done will be high (increasing NHS and patient costs).	Thank you for your comment. The diagnostic pathways are designed to provide people with asthma the correct diagnosis at the time of initial presentation. They are based on cost-effectiveness, not cost alone with the effectiveness estimates derived from systematic reviews of the literature. The studies which inform this guideline are generally not RCT's, and the well-known phenomenon of unrepresentative recruitment in trials of new drugs may not apply. Many of the studies recruited consecutive patients attending clinics for diagnosis. Moreover, the health-economic analysis included sensitivity analyses which tested the robustness of the model under varying circumstances. We also note the feasibility study which was performed in primary care in England (Appendix Q).
GP Virtual Forum	Short	General	General	We welcome the guidance and agree with many comments in the introduction regarding the over- and under- diagnosis of the condition.	Thank you for your comment.
GP Virtual Forum	Short	General	General	There is significant challenge for primary care. Some practices are not fully confident with spirometry let alone FeNO. There are resource implications for practices and commissioners: FeNO monitors, disposables, and the skilled staff needed to interpret all results	Thank you for your comment. We agree this guideline calls for a change in practice; however there is evidence to show that asthma diagnosis needs to improve. Whilst we acknowledge there will be initial upfront costs to be met, if implemented, the guideline will improve patient outcomes and is cost-effective to the NHS in the long-term; NICE's cost impact assessment projects a saving of approximately £14 million per year in England, before implementation costs. It is outside of the GC's remit to recommend how services should be organised; some may refer to secondary care or some CCGs may support individual GP practices to implement the guideline e.g. purchase of FeNO machines, to achieve cost savings through economies of scale.
GP Virtual Forum	Short	15-17	Algorithm	In view of our comments above, it would be helpful to have an algorithm for diagnosis where FeNO testing is not yet available.	Thank you for your comment. However, FeNO was shown to be a useful test in the diagnosis of asthma therefore it would be wrong to omit it from a diagnostic algorithm.
GP Virtual Forum	Short	4	12	We welcome the section on identifying and documenting occupational causes. We are concerned, however, that occupational asthma specialists may not be easily accessed, and in their absence this is not a realistic suggestion.	Thank you for your comment. As with other implementation issues, this is not a reason not to recommend referral to occupational asthma specialists and inclusion in the guideline may be the driver for change needed to improve this service provision.
GP Virtual Forum	Short	5	1	Children aged between 5 and 10 will not consistently and reliably perform spirometry, and the economic costs of repeating this test every six months should be considered.	Thank you for your comment. This cost was considered when the committee considered the use of spirometry in younger children.
GP Virtual Forum	Short	5	7	Asthma is likely to move out of practices to larger scale settings (hubs or similar) to enable clear diagnosis and initial education/self-management plans. We hope that this will be an interim measure for those practices that wish to provide a local service, until they obtain equipment and expertise. Ongoing management should remain a local responsibility.	Thank you for your comment.
GP Virtual Forum	Short	5	7	Spirometry is routine in most practices and patients generally like investigation locally. Although working at scale has benefits, it is not a one size fits all solution, especially in rural areas with poor public transport connections. This may cause further delay to the diagnosis and appropriate treatment of symptoms. We are uncomfortable with NICE recommending (although we appreciate it is a "consider") how services are implemented and commissioned.	Thank you for your comment. The recommendation on diagnostic hubs is a suggestion only about how the guideline could be implemented. Whilst we acknowledge that this particular recommendation on service delivery is not based on a formal evidence review, NICE does produce service delivery guidelines that make recommendations on how services are implemented and commissioned for specific conditions. Please see this link to the NICE website on its range of service delivery guidance: https://www.nice.org.uk/guidance/service-delivery--organisation-and-staffing However, we are not necessarily recommending that hubs should be large – in some places they may consist of a few practices linking for this purpose.

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GP Virtual Forum	Short	5	13	The use of FeNO in the diagnosis of asthma is interesting and the evidence presented supports its use in the diagnosis of asthma. It is, however, a challenge when surgeries do not own machines where this can be measured.	Thank you for your comment. We agree it is a challenge but not insurmountable. We hope CCG's will support primary care in making FeNO analysers available.
Intermedical (UK) Ltd	Full	149	9	We are concerned about the wording used to describe how easy the devices are to use. The current wording is as follows: "*The project cited positive feedback for the NIOX VERO machine with very good patient compliance. All sites agreed that the device was easy to use and training was not lengthy (less than for spirometery). Moreover, fewer patients were unable to complete FeNO measurement than spirometry (5 vs 9). However it was noted that the NObreath device was difficult to use."* We are challenging the above statement highlighted in yellow for the reasons as per below: • The feasibility study (Appendix Q / Page 851 / lines 3 to 5 inclusive) indicates that '*there is no formal assessment of competency for the use of the FeNO devices, but this was reported to be straightforward by the sites and training took less than 1 hour*.' This finding confirms that the FeNO devices (in general) used in the feasibility study were in fact "straightforward" and doesn't make any reference to the NObreath being difficult to use. • The feasibility study (Appendix Q / Page 851 / lines 8 and 9) also says '*Six sites stated that FeNO was a welcome addition to the diagnostic process and an easy test to carry out, with positive feedback from patients.*' This finding further concludes that at least one out of the two sites using the NObreath also shared the same view that it was an easy test to carry out. Only two out of the seven sites that were recruited for the study used the NObreath. To make the statement "difficult to use" in the full guidelines is deemed to be an unfair assessment to the operational use of the NObreath, contradicts the feasibility study findings and potentially very damaging to future use of the NObreath in GP surgeries. Currently, hundreds of sites use the NObreath on a daily basis and we have not received any negative feedback from them on the usage of the device. We feel the "difficult to use" statement is written based on one site's feedback and is not a true and fair representation of how easy the NObreath is to use.	Thank you for your comment. The LETR has been amended to remove brand names of FeNO machines. The feasibility study reports the sites experiences but does not detail which device the comments were made about.

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				We believe the statement on page 149 portrays a biased view of the devices and this appears to conflict with many other sources, including NICE Guidance specifically written to evaluate the device competency. We would therefore request that the wording is removed from the final guidance.	
Intermedical (UK) Ltd	Appen dix Q	851	Table 7	Servicing of the NObreath has been changed to a 5 year plan following post marketing surveillance carried out by the manufacturer also failure rates of the sensor and internal components being negligible. We would like the 'Bi-annual' to '5 year' please.	Thank you for your comment. This table has been removed from the appendix and the information incorporated into the NICE Resource Impact Assessment where more detail about device costs, maintenance and need for replacements is presented.
Intermedical (UK) Ltd	Appen dix Q	851	Table 7	The table shown has omitted that the NIOX VERO has an operational lifetime of 5 years or 15,000 tests, whichever comes first and must be replaced with a new device as this point (Page 2 of NIOX VERO manual) http://www.niox.com/Global/NIOX%20VERO%20User%20Manuals/000191-09%20NIOX%20VERO_User%20Manual%20English.pdf The NObreath is unlimited by time or usage. This information should be added to the 'Other costs' column in Table 7.	Thank you for your comment. This table has been removed from the appendix and the information incorporated into the NICE Resource Impact Assessment where more detail about device costs, maintenance and need for replacements is presented.
Intermedical (UK) Ltd	Appen dix Q	851	Table 7	The NIOX VERO test kits have an operational life of 'Maximum 12 months after opening the package and installed in the NIOX VERO or expiration date as stated on the sensor, whichever comes first' any unused tests at this time will be lost (Page 2 of NIOX VERO manual) http://www.niox.com/Global/NIOX%20VERO%20User%20Manuals/000191-09%20NIOX%20VERO_User%20Manual%20English.pdf The NOBreath test kits are unlimited by time or usage. This information should be added to the 'Filters' column in Table 7 please.	Thank you for your comment. This table has been removed from the appendix and the information incorporated into the NICE Resource Impact Assessment where more detail about device costs, maintenance and need for replacements is presented.
Napp Pharmaceuti cals Limited	Short	5	7	**Section 1.3.1 diagnostic hubs** Many of the services outlined in the guidance would benefit from economies of scale and as noted, improve the practicality of implementing the recommendations. There is no discussion of how these diagnostic hubs will be created, lead, funded or where they will be located. With regard to location many patients already do not attend their annual asthma review and given the variable nature of asthma encouraging patients to travel further to "diagnostic hubs" will not be practical for the majority.	Thank you for your comment. Diagnostic hubs might come in a variety of sizes and locations depending on local variables. It would be inappropriate for us to suggest an optimum configuration.
Napp Pharmaceuti cals Limited	Short	5	14	**Section 1.3.2 Fractional exhaled nitric oxide** In the final section of the guideline there are several challenges highlighted with regard to implementing this guideline, a key point being the availability of FeNO testing given the strong focus applied to FeNO throughout. As acknowledged in the guideline FeNO testing and effective spirometry use are not currently common within primary care and to achieve the standard set out in this guidance within primary care	Thank you for your comment. We agree this guideline calls for a change in practice, however there is evidence to show that asthma diagnosis needs to improve. Whilst we acknowledge there will be initial upfront costs to be met, if implemented, the guideline will improve patient outcomes and is cost-effective to the NHS in the long-term; NICE's cost impact assessment projects a saving of approximately £14 million per year in England, before implementation costs. It is outside of the GC's remit to recommend how services should be organised; some may refer to secondary care or some CCGs may support individual GP practices to implement the guideline e.g. purchase of FeNO machines, to achieve cost savings through economies of scale.

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				would require considerable changes to the way asthma is currently diagnosed and monitored, with large amounts of funding required. Given the current funding gap within the NHS this is not likely to be currently feasible. Given the lack of availability of FeNO testing, effective spirometry and cost associated with implementing both, this may lead to patients traditionally treated in primary care being pushed into secondary care and increasing the burden on the NHS whilst potentially deskilling primary care asthma management.	We disagree that performing tests outside an individual primary care will drive patients to secondary care. Primary care doctors already use other services for diagnostic tests (e.g. x-rays) but receive the results to act on themselves.
National Paediatric Respiratory and Allergy Nurses Group	Full	general		We are concerned that the principle of "probability" is not clearly identified as a solid foundation upon which to suspect asthma, particularly in children. The diagnostic algorithm and some tables are quite complicated	Thank you for your comment. The BTS/SIGN guideline on asthma tries to build an algorithm around probability following history-taking but this has not been adopted as part of routine clinical practice. We agree that a relevant history is important in deciding who might have asthma.
National Paediatric Respiratory and Allergy Nurses Group	Full	General	Section 9	The evidence from the studies is noted to be inconsistent and bias – suggest further well-structured studies into this important area which accounts for new onset asthma in adults	Thank you for your comment. We agree and we have suggested in the Full Guideline that further research is required..
National Paediatric Respiratory and Allergy Nurses Group	Full	54-57	general	It is of concern that there is limited evidence for children and no evidence underpinning recommendations for diagnosis in 5-16 year olds	Thank you for your comment. We agree that the evidence base for children and young people was either lacking or of low quality; hence the GC made a high-priority research recommendation on asthma diagnosis in children and young people. We hope that high quality studies on this topic will be conducted to inform future updates of the guideline.
National Paediatric Respiratory and Allergy Nurses Group	Full	17	6 .3	Agree with practical disadvantages of obtaining a blood test. Could be relatively cost effective if bloods being obtained for other routine tests at point of diagnosis or after referral to specialist care e.g. sIgE's, VIT D so could consider in these circumstances Agree that to be of benefit the test would need to lead to a change in the diagnostic decision. May help in determining treatment in difficult to treat problematic asthma once referred to specialist care. Eosinophil counts can be high in other other conditions therefore results must be interpreted with care and in conjunction with other diagnostic tests.	Thank you for your comment. We agree it would not do any harm to order an eosinophil count as part of other routine blood tests, but the evidence did not support doing an eosinophil count specifically to diagnose asthma.
National Paediatric Respiratory and Allergy Nurses Group	Full	18	4 current practice	Agree that a strategy that involves not carrying out any tests and diagnosing without the use of objective tests is cheaper however the cost of potentially over diagnosing is great - cost of medication, cost of on-going symptoms / GP visits as symptoms not better with asthma treatment, regular asthma reviews that may not be helpful etc	Thank you for your comment. We agree; the aim of this guideline is to improve the accuracy of asthma diagnosis.
National Paediatric Respiratory and Allergy Nurses Group	Full	18	6.3	Agree that the role of histamine CT's tests is only helpful if a diagnosis is uncertain and referral to specialist centre being made. CT's only suitable for older children and adults who are able to perform reproducible spirometry. Agree that currently CT's are only available in secondary (& tertiary care). Not required in primary care - practicalities and related costs in primary care would not be cost effective.	Thank you for your comment.

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National Paediatric Respiratory and Allergy Nurses Group	Full	19	6	The risk of severe bronchospasm from a mannitol challenge therefore must only be considered when all other tests are inconclusive. Can only be performed in secondary / tertiary care with resuscitation facilities available. Not safe in primary care therefore should carefully consider the scope for performing in primary care in view of other safer diagnostic tests available. Agree that in children the clinical evidence informing the diagnostic accuracy of mannitol tests was poor and cost high therefore not a recommended diagnostic test at current time.	Thank you for your comment.
National Paediatric Respiratory and Allergy Nurses Group	Full	44	general	Most HCPs do not have a good knowledge and understanding of FENO and the normal range is affected by a variety of factors. We are concerned with the recommendation to regard readings greater than 35ppb in a child as a positive test as this is misleading and could lead to errors in diagnosis	Thank you for your comment. The GC acknowledge that there is no perfect sharp cut-off point for FeNO, but this applies to many tests used in medicine yet they still have value if used in clinical context. The GC chose the diagnostic cut-off values for adults and children based on summary ROC curves which are provided in appendix J sub-section 10.1.1 on page 457. The diagnostic cut-off values recommended in this guideline are the same as those recommended by the BTS/SIGN guideline on asthma (page 18). There are no new data that suggest different cut-off values should be used to indicate a positive test. Moreover, this guideline does not recommend using any single test to diagnose asthma, therefore a diagnosis of asthma will be supported by evidence from other objective tests and not on the basis of a FeNO test alone.
National Paediatric Respiratory and Allergy Nurses Group	full	44	5	Q1 This recommendation will be difficult to meet because most 5 year olds cannot perform objective tests and tests in children are often not reliably performed until 8-10 years of age Q3 Guidance to CCGs about commissioning and access arrangements for paediatric diagnostics as this usually falls into the specialist commissioning area	Thank you for your comment. We agree that performing tests in this age group can be more challenging than in adults, but this is true of tests for other conditions, not just asthma; it doesn't mean the tests should not be done. The GC has made specific recommendations in children and young people around what to do if they cannot perform the tests at that point in time. The GC cannot give specific advice about arrangements for paediatric diagnostics as this will vary depending on existing facilities, but diagnostic hubs for paediatrics might also be appropriate.
National Paediatric Respiratory and Allergy Nurses Group	Full	44	15	More detail needed about the factors affecting FENO levels	Thank you for your comment. This is provided in the LETR for FeNO on page 147, first paragraph, of the full guideline.
National Paediatric Respiratory and Allergy Nurses Group	Full	44	17	Q1 and Q3 FENO is not used in primary care or in many secondary care centres and it is still too expensive for widespread use	Thank you for your comment. We agree that FeNO is currently not widely used but this applies to any new test and does not constitute a reason for failing to recommend its use. Regarding cost, see above response to your similar comment in ID99.
National Paediatric Respiratory and Allergy Nurses Group	Full	44	30	Does not reflect LLN for children	Thank you for your comment. Please see the footnote. We have now changed this recommendation.
National Paediatric Respiratory and Allergy Nurses Group	Full	45	1	Why is this "consider" not offer, if a child can perform spirometry and it is obstructive (based on age appropriate LLN) why would you not recommend BDR	Thank you for your comment. The wording of the recommendation is based on the strength of the evidence regarding the diagnostic accuracy of the test, and not the child's ability to perform it.

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National Paediatric Respiratory and Allergy Nurses Group	Full	46	general	We welcome the recognition of PEF variability as a valuable tool in the diagnosis of asthma but are concerned about the level of emphasis placed upon the role of FENO in diagnosis. This guideline seems to biased toward a test that is poorly understood, expensive and is largely inaccessible	Thank you for your comment. The review of evidence on the diagnostic accuracy of FeNO showed it to be better than PEF variability, and in particular to be a much more sensitive test.
National Paediatric Respiratory and Allergy Nurses Group	Full	46	9	It is of concern that there is limited evidence for children and no evidence underpinning recommendations for diagnosis in 5-16 year olds	Thank you for your comment. We agree that the evidence base for children and young people was either lacking or of low quality; hence the GC made a high-priority research recommendation on asthma diagnosis in children and young people. We hope that high quality studies on this topic will be conducted to inform future updates of the guideline.
National Paediatric Respiratory and Allergy Nurses Group	Full	47	Table 7	LLN for obstruction should be more specific	Thank you for your comment. In practice the LLN is generated by software in spirometers or is calculated by lung function laboratories.
National Paediatric Respiratory and Allergy Nurses Group	Full	71	3	In the opening sentence symptoms of cough, wheeze and chest tightness are referred to – however in table 17 tight chest is replaced with breathlessness. Breathlessness with activity is normal for any individual so suggest this is amended to reflect this – noted in 8.6	Thank you for your comment. 'Breathlessness' has been clarified with '(over and above what you would expect during exercise)' in table 17.
National Paediatric Respiratory and Allergy Nurses Group	Full	76	8.6	Suggest that a research study specific to children regarding exercise and asthma would be important. There is no mention of breathing disorders or obesity which may be the cause of the symptoms rather than asthma	Thank you for your comment. The GC has made this research recommendation – please see appendix N (page 672) of the full guideline, or the short version page 22. Regarding your second point, performing the objective tests for asthma would allow for early identification of when symptoms are not due to asthma.
National Paediatric Respiratory and Allergy Nurses Group	Full	217	37	Page 217, line 37 they need to change 'an' to 'a' as in 'a borderline' rather than 'an borderline'.	Thank you for your comment. This change has been made.
NHS Durham Dales Easington and Sedgefield CCG	Short	General	General	We feel that there is significant overlap with the SIGN/ BTS guidance and caution that guidelines that interact produce problems for implementation (compare UTI in children guidance CG54 in the North-East). We recommend that the guidelines are aligned where possible.	Thank you for your comment. The GC acknowledges that there are differences in the remits and methodologies used by both NICE and BTS/SIGN. For example, NICE uses GRADE methodology, considers cost-effectiveness evidence. Due to these differences in remit and methodology a collaborative guideline was not possible..Notwithstanding this, the GC agree with you that the recommendations in both guidelines are broadly similar; both guidelines recommend doing a spirometry and FeNO test to diagnose asthma and that clinical history-taking is an important part of the assessment. NICE and BTS/SIGN are discussing how we might bring the two guidelines together
NHS Durham Dales Easington and Sedgefield CCG	Short	15-17		The algorithms are very precise and clear However, attention should still be paid to ensuing plenty of education to ensure they are used appropriately	Thank you for your comment. We agree.
NHS Durham Dales	Short	4-5	22-4	The liberal approach to children is welcome as many will find both spirometry and FeNO difficult and clinicians' judgement should still	Thank you for your comment. The GC did not consider PEF measurement showed sufficient diagnostic accuracy to warrant recommending it first-line.

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Easington and Sedgefield CCG				be a very important part of diagnosis. However, the need to repeat objective tests (especially spirometry) is likely to be resource-hungry and the use of peak flow tests as an alternative should be emphasised.	
NHS Durham Dales Easington and Sedgefield CCG	Short	6/7	23 /3	Can you expand on '20% variability' traditionally this could mean peak-trough values (eg before and after treatment), which fit the pattern of patient presentations to GPs	Thank you for your question. When we refer to PEF variability we are referring to the amount of variation seen in PEF measurements when they are recorded twice a day or more for a week or more. There does not need to be an element of "before and after treatment " in this, although a decrease in variability could be used to assess the effect of treatment.
NHS Durham Dales Easington and Sedgefield CCG	Short	5	8	Diagnostic hubs allow for pooling of resources and expertise but aren't likely to be universally accessible especially in an acute presentation – though this is true of rural areas, some urban areas may also find the hubs to be a barrier	Thank you for your comment. We agree it may not work in all localities.
NHS Durham Dales Easington and Sedgefield CCG	Short	5	13	Karrasch et al (Thorax 2016) concludes: 'There appears to be a fair accuracy of FENO for making the diagnosis of asthma. The overall specificity was higher than sensitivity, which indicates a higher diagnostic potential for ruling in than for ruling out the diagnosis of asthma.' In General practice, sensitivity is more important in diagnostic management. The algorithm explains its position in diagnosis better than the text (as an add-on test)	Thank you for your comment. FeNO is more specific than sensitive, but is more sensitive than either bronchodilator reversibility or PEF variability.
NHS Durham Dales Easington and Sedgefield CCG	Short	6	1	Spirometry – less accessible and less tolerable in an acute presentation – which is when most GP diagnoses are made. If delayed, spirometry (+/- reversibility) will often be normal. It probably has greater significance for treatment (and future acute presentation) planning than acute management. It is important to encourage a provisional diagnosis in the acute phase. The guidelines produce a 'catch 22' – treat and the tests become negative; don't treat as patients may come to harm.	Thank you for your comment. Both spirometry and measurement of FeNO can be performed during an acute presentation. The proposed scenario was not seen in the implementation pilot. We do not agree that most people present with an asthma attack so acute as to rule out spirometry. In those who do we do not recommend against a **provisional** diagnosis, but we suggest that this should be confirmed with objective tests at a later stage when possible.
NHS Durham Dales Easington and Sedgefield CCG	Short	13	13	The asthma control test appears simple and we'd commend this for use in General Practice. Simple questionnaires are more likely to be implemented effectively.	Thank you for your comment.
NHS England	Appendix Q Feasibility report	General		A feasibility study in seven general practices to see if the algorithm could be followed. Practices were provided with spirometry training support and free FeNO machines. Whilst it appears as if it was possible to follow the algorithm, the study raised important issues:- • In most cases spirometry was normal at the time even in patients diagnosed with asthma and did not contribute to the diagnostic process. • Smoking avoidance for 48hrs prior to FeNO measurement was difficult None of the practices had local access to bronchial challenge testing if that was required for confirmation.	Thank you for your comment. We agree that spirometry was normal in most people within the feasibility study, but 18% had obstructive spirometry so the pick-up is not negligible, and the value of the result is considerable in those people. We also note that BTS/SIGN suggest using spirometry in asthma diagnosis. The GC do not consider that smoking is a significant enough reason not to do a FeNO test, as current smoking reduces, rather than removes, the signal. The prevalence of smoking in the general population is around 20% (and is similar in people with asthma); therefore the majority of people performing a FENO test with suspected asthma are not affected at all, and in those who smoke a high FeNO level is helpful. The GC acknowledges that currently access to bronchial challenge tests is limited and have made a recommendation on what to do if a bronchial challenge test is not available. However, bronchial challenge is the single most accurate diagnostic test for asthma. The GC has tried to limit it to those patients who need it most. Recommending it in this guideline will hopefully drive the necessary change in service provision.

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NHS England	Appendix Q Feasibility report	General		The success of this guideline will depend upon the willingness or capacity of primary care services to implement. This is unlikely to happen in the absence of significant financial incentive. The likely result in the short term will be an increase in secondary care referrals for diagnosis.	Thank you for your comment. We agree, but improvements in asthma diagnosis need to be made and we hope this guideline will be a driver for change in this service provision. The NICE adoption team are planning to develop a web based adoption support resource, which shares learning from the sites involved in the feasibility study to support those in practice responsible for implementing this guideline.
NHS England	Short/ Full	General		NHSEngland welcomes any guideline that improves diagnostic accuracy in patients with lung disease. This guideline covering adults and children is a revised version of the original which was presented in draft form over two years ago. There has been some modification but the basic recommendations around the use of quality-assured spirometry and exhaled nitric oxide measurement (FeNO) remain unchanged. The revision is supported by an implementation feasibility study. The guideline recommends a distinctly new approach to asthma diagnosis which carries considerable risk, particularly around implementation. This guideline is likely to generate significant controversy for the reasons set out below.	Thank you for your comment.
NHS England	Short/ Full	General		Other current evidence-based asthma guidelines do not recommend the routine use of FeNO for diagnosis. Both GINA and BTS/SIGN (NICE approved) are clear on this point. This contradiction will cause some confusion.	Thank you for your comment. We acknowledge this difference in relation to FeNO. It is not appropriate for us to speculate on why the other groups did not recommend use of FeNO, but we will point out that they recommend using spirometry, with bronchodilator reversibility (when appropriate), yet this test has a lower sensitivity and specificity for asthma diagnosis.
NHS England	Short/ Full	General		The recommendations for children appear to be derived from evidence from adults. A forthcoming paper by Murray et al in the Lancet Child and Adolescent has trialled the NICE algorithm in children and found it to be unhelpful. An accompanying editorial suggests that evidence is lacking.	Thank you for your comment. The GC cannot comment on a study that is yet to be published and not in the public domain.
NHS England	Short/ Full	General		The attempt to improve diagnostic accuracy is to be applauded and it may be that the proposed pathway has value. However, this will not be immediately obvious and careful evaluation of the guideline implementation will be required. It is very unlikely that every general practice will be willing or able to conduct the diagnostic pathway. NICE recommends the development of diagnostic hubs within federations or larger primary care organisations. This is in line with policy and the roll-out of diagnostic quality spirometry. It will inevitably result in short term increases in secondary care referrals and possibly some delays in treatment.	Thank you for your comment. We agree this guideline calls for a change in practice, but there is evidence to show that asthma diagnosis needs to improve. Whilst we acknowledge there will be initial upfront costs to be met, if implemented, the guideline will improve patient outcomes and is cost-effective to the NHS in the long-term; NICE's cost impact assessment projects a saving of approximately £14 million per year in England, before implementation costs. It is outside of the GC's remit to recommend how services should be organised; some may refer to secondary care or some CCGs may support individual GP practices to implement the guideline e.g. purchase of FeNO machines, to achieve cost savings through economies of scale.
NHS Tower Hamlets CCG	Short	General	General	As stated in the guideline 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. This leads to some uncertainty on the value added of this test.	Thank you for your comment. The review of evidence on the diagnostic accuracy of FeNO showed it is a useful test. We agree that it is not perfect on its own, as in the example you cite, but nor is any other single test. The guideline promotes seeking both airway inflammation and airway reversibility.
NHS Tower Hamlets CCG	Short version	General	General	We are concerned about the appointment burden for patients, the additional costs & the burden to primary care. Given the current pressures on primary care we would not support anything adding additional pressures where the value add is still so unclear.	Thank you for your comment. The analysis described in the guideline shows that implementing this guidance would be cost-effective. We acknowledge that without action by commissioners the benefit would be to the NHS as a whole whilst GP's would bear the cost of introducing the new tests. The GC hope that CCGs will recognise this and provide support to primary care to deliver the changes.
NHS Tower Hamlets CCG	Short version	General	General	There may be practicalities of implementing this with diverse ethnic populations. Has this been considered?	Thank you for your comment. GC The GC did not find evidence that the diagnostic tests performed differently in different ethnic groups, although admittedly this is an absence of evidence rather than evidence of homogeneity.

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NHS Tower Hamlets CCG	Short version	General	General	We feel there may be benefits to this approach however the business case for this needs to be made more clearly. For example questions we have are: What is the impact on the whole asthma pathway? - How many visits would the patient need to make? - Is it likely to increase or decrease diagnosis of asthma? - What are the knock on effects in steroid inhaler use and prescribing budgets? - Are there potential opportunities from decreased referrals as patients are fully assessed in primary care? What is the most appropriate footprint to roll this out in? Are there benefits to rolling this out at an STP level?	Thank you for your comment. NICE guidelines on other conditions are published without initial testing. This guideline on asthma has gone a step further and piloted the algorithms for 6 months and demonstrated that they are implementable. However, that sample is insufficient to provide definite answers to your questions. Our best guesses would be: - Including the visit at which symptoms are first presented, probably 3 in most cases - Probably decrease - A reduction is likely - This one is very hard to answer. GP's will have extra tests available (specifically FeNO) but may request more challenge tetsts
NHS Tower Hamlets CCG	Short version	General	General	We are concerned about the potential additional diagnostic costs for obtaining, maintaining, training and interpreting the machines in primary care. How many machines per 1000 population will be needed? What is the cost of the machines?	Thank you for your comment. It is outside of the GC's remit to recommend how services should be organised; however, the GC have suggested that there would be economies of scale by use of diagnostic hubs.
NHS Tower Hamlets CCG	Short version	18	11	This says putting recommendations into practice can take time….most effective when aligned with local priorities Question: If this guideline is approved how long would CCGs have to implement changes before having to justify deviation from NICE? We understand there is limited experience of using this in secondary care let alone in GP practices. Ideally we would like the opportunity to pilot this with a few practices before deciding to roll this out. All tests will require an additional organisational response, spend and culture change which will take time.	Thank you for your comment. The adoption team are developing an adoption resource to be published on the NICE website after guideline publication. You may wish to refer to this.
North West Severe Asthma Network	Full	Introduction		Some very specific examples relating to the rationale for the guideline as laid out on the introduction: P13 l20-22. Re: the evidence for "underdiagnosis". Whilst we agree that this is likely to be a problem, the text as written betrays a basic and worrying misunderstanding of both statistics and respiratory physiology. The first sentence implies that airflow obstruction is 100% sensitive and specific for asthma. The following sentence is also nonsense, but for a different reason. P13 l29-30 "there is no single test that can definitively diagnose asthma" – what is the evidence for this? What would be the more likely alternative diagnosis for example in a patient with typical symptoms and a positive bronchial challenge test, even with other negative tests? P13 l36 "Testing for airway inflammation is increasingly used as a diagnostic strategy in clinical practice" – where is the evidence?	Thank you for your comment. There is a considerable body of evidence that incorrect diagnosis of people presenting with respiratory symptoms occurs from cross sectional studies. The GC recognise the concern for potential misinterpretation regarding the sentence and it has been removed. Asthma is a syndrome comprising variable airway inflammation, airways obstruction and airways hyperreactivity. Bronchial challenge testing is not 100% sensitive and specific for asthma. For example BHR can occur in patients with pulmonary sarcoidosis. The GC agree with your assertion that testing for airways inflammation is increasingly used and the wording of the introduction is compatible with this. The sentence on P14 to which you refer means that the guideline aims to identify the most clinically effective and most cost-effective way of diagnosing and monitoring asthma i.e we looked at clinical effectiveness papers and cost-effectiveness papers where available, and performed our own cost-effectiveness analysis. "Most effective" does not have a definition as such, but in the context of this guideline we are particularly interested in the most accurate diagnostic pathway for asthma, which should result in the best use of therapy and best patient outcomes.

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				Whilst its use is rising in secondary care, we feel that this is not true in primary care, where most asthma is diagnosed. P14 l5-7 "The aim of this guideline is, therefore, 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". What is meant by "the most clinical….way"? And how is "most effective" defined?	
North West Severe Asthma Network	Full	16	13-15	"Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate". We note that Prof Thomas' COI with Aerocrine / Circassia has "expired". This may be true as far as the rules for NICE are concerned, but as he's still promoting it on their website (http://www.niox.com/en/FeNO-Testing-for-UK-Primary-Care/) it would not appear that way from a more general / lay perspective. Our comments on the previous draft are still therefore relevant: : o "First (even though he withdrew from 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) o 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."	Thank you for your comment. Professor Mike Thomas withdrew from discussions on FeNO and the health economic model when the guideline was being formulated. The recommendations on FeNO have not changed since his conflicts of interest expired; therefore it cannot be said that he has influenced the recommendations as an individual. Our response to your comments from 2015 are as follows: Professor Mike Thomas's conflict of interest was managed in accordance with the NICE declarations of interest policy. We disagree that there was insufficient expertise on the GC 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. We would also note that there are no 'key' members of the GC; all GC members have equal standing and no single GC member's opinion takes precedence over another. The GC has no input or control over Aerocrine's marketing strategy. However, we believe that the quote from their website refers to the NICE DAP on FeNO, which is final published guidance, not this draft NICE clinical guideline.
North West Severe Asthma Network	Full	40	Algorithm A	- We agree that symptoms alone should not be used to diagnose asthma; the second box under that (re: syx after exercise / hx of atopy) is therefore unnecessary - "Treat people immediately if acutely unwell": we agree but there should be guidance on what to use, as this will potentially compromise further testing. - "do not offer….exercise challenge (..17 and over) implies it could be offered to under 17's - Right middle box "if indicated…" – what are the indications?	Thank you for your comment. We agree there is some degree of repetition here as this recommendation on 'symptoms after exercise' was derived from a specific review on symptoms after exercise; we have removed this from the algorithm. Regarding your point about guidance on what to use to treat people who are acutely unwell, we agree that this could impact on subsequent testing. We have added a recommendation to 'Be aware that the results of spirometry and FeNO measurement may be affected in people who have been treated empirically with inhaled corticosteroids'. Regarding your point about exercise challenge tests in under 17s, we agree that this test could be offered to under 17s based on the review of evidence, hence the wording of this recommendation; the evidence showed that this test was not clinically and cost effective in adults given the availability of better tests in this population

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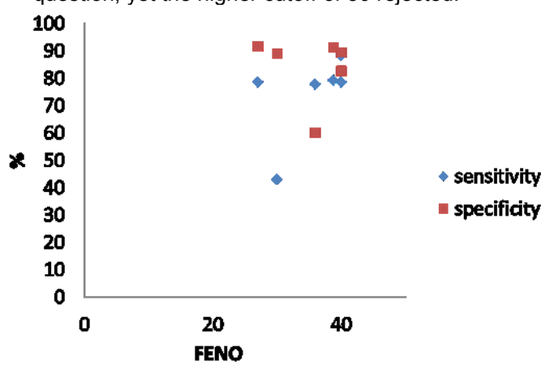
					group, therefore the GC made a 'Do not' recommendation in adults. But there was no evidence to suggest that it should not be done in children. Regarding your point about skin prick tests, 'if indicated' has been removed from the recommendation.
North West Severe Asthma Network	Full	40	11	We agree with the need for diagnostic hubs, but feel these will be essential for implementation, not just "to be considered". The very limited data gathered in the Feasibility Study in Appendix Q (which only included 33 patients with asthma) clearly demonstrates that even in these keen, dynamic primary care practices the guidelines are not implementable – the algorithms were not followed in nearly half of cases. This study further demonstrates the problems primary care have interpreting spirometry results, as none of the included patients were reported to have a restrictive pattern – surely this cannot be true?	Thank you for your comment. The recommendation on diagnostic hubs is based on GC consensus rather than on evidence. Using NICE methodology, the strength of the evidence behind the recommendation requires us to use the word 'consider'. The feasibility study reflected real life implementation of a clinical guideline where patient factors and clinical judgement influence the final action for each individual patient. Where there were deviations these were most commonly because practitioners completed an additional test or peak flow measurements were missed, not because the algorithm could not be implemented.
North West Severe Asthma Network	Full	42	Algorithm C	- "airway reversibility" – should be "reversible airflow obstruction". - FENO. We cannot see how the cutoffs, particularly of 40, are justified. If FENO in this range were to be useful and biologically valid one would expect its specificity to increase and sensitivity to decrease with increasing FENO level. However looking at the data presented in table 48, p142, this is not the case. The chart below shows these points plotted. The specificity essentially remains the same (around 90%) between FENO levels of 27 and 40ppb (apart from the two obviously outlying points). This is clearly nonsensical and the only explanation must be that the study's methodologies and/or populations make them incomparable, and therefore not fit for purpose here. It is also not explained why the American Thoracic Society's lower cutoff here has been accepted without question, yet the higher cutoff of 50 rejected.  - PEF variability. It is not clear how NICE would like this calculated. Over how many weeks, and using what formula? - In the "unobstructed" group: if BCT is unavailable then treatment can be started on the basis of raised FENO alone, in contradiction to the statement "do not diagnose asthma based	Thank you for your comment. This change has been made. The GC acknowledge that there is an acceptable range of values that would constitute a positive FeNO test and there is no perfect cut-off. Other cut-offs were not shown to be cost-effective. The GC chose the diagnostic cut-off values for adults and children based on summary ROC curves which are provided in appendix J sub-section 10.1.1 on page 457. The diagnostic cut-off values recommended in this guideline are the same as those cited by the BTS/SIGN guideline on asthma (page 18). There are no new data that suggest different cut-off values should be used to indicate a positive test. Moreover, this guideline does not recommend using any single test to diagnose asthma, therefore a diagnosis of asthma will be supported by evidence from other objective tests and not on the basis of a FeNO test alone. Regarding PEFv, we have added to the LETR that if GPs have access to computerised tools for calculating PEFv, amplitude as a percentage of mean is the best measure to use. In practice amplitude as a percent of highest value is easier to calculate and is acceptable. We agree that the current difficulty in accessing bronchial challenge testing will mean that some people need to be diagnosed and treated on the basis of a single positive test. The GC hope that pointing out its value in this guideline will increase availability of challenge testing in future. We have removed the recommendation on diagnosing on the basis of a single result. Regarding your last point about reversible airflow obstruction and low FeNO, it is hard to capture all the possibilities here, and as stated in the guideline the clinical history will be important. We agree with the point you are making insofar as the conclusion might still be that the person has an atypical form of asthma, but if, for example, the reversibility was borderline positive and the history more of a productive cough with infective episodes, one would consider bronchiectasis as an alternative.

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				on any single test alone". Unless "Response to treatment" is objectively defined. - Reversible airflow obstruction is a defining feature of asthma. Yet if a patient's FENO is <25 an alternative diagnosis should be considered. What would that be? If someone has reversible airflow obstruction and compatible symptoms then they have asthma. The low FENO suggests it may not be very sensitive to steroids, but that does not mean it is not asthma	
North West Severe Asthma Network	Full	197	general	The document would be benefit from a clearer and more coherent definition of what is meant by "asthma control". The sections variously consider symptom control, unscheduled healthcare use, mortality and so on. The relative weighting of these in decision making is not explicit.	Thank you for your comment. Asthma control is a composite of all the factors that you mention. The section you refer to is a review of the available questionnaires for measuring control, and although they have features in common the exact calculation of control obviously differs between them.
North West Severe Asthma Network	Full	243	general	The section on blood eosinophils highlights a broader point in these guidelines. As is mentioned, the lack of a randomised controlled trial does not mean a lack of evidence. We imagine this was a point raised strongly by the clinicians present. As is often highlighted, people with asthma who enter into RCTs are usually not typical of the wider asthma population, and randomising them to an arm where their blood eosinophils were ignored would not seem to be an appropriate way of generating generalizable results (certainly it would be challenging to get funded). We encourage NICE to think more carefully about the usefulness of presenting data generated outside RCTs.	Thank you for your comment. We acknowledge the point you make, but you will equally be aware of the dangers of studying a less well-defined population particularly in a disease such as asthma which can be difficult to diagnose.
North West Severe Asthma Network	Full	256	General	Following the above point, the section on adherence includes only two studies in adults as it is limited to recent RCTs. We are therefore left with the clumsy "no clinical recommendation" statement. This will be interpreted by some that medical concordance is not especially important in asthma, as few people who are not especially interested in the disease will read the whole text of the guideline.	Thank you for your comment. Based on the available evidence the GC did not make a clinical recommendation but made a research recommendation to guide future updates of the guideline. The question posed was whether it was possible to advise on how best to measure adherence, not whether or not it was important. The GC were sorry not to be able to recommend how to do this, as the LETR makes clear. Nevertheless, the guideline includes a clear recommendation to take adherence into account in the first recommendation in the monitoring section, and this is also part of the advice in the first recommendation of the companion NICE Guideline on Asthma Management, so the not especially interested people to whom you refer should not be in any doubt about the importance of this.
North West Severe Asthma Network	Full	291	General	We suggest the section on tele-healthcare requires further thought. We agree with the observation that this is a heterogeneous group of interventions, and we note the sub-comparisons were introduced part way through the process. However, "tele-health" is an ever more blurred concept and we would encourage the placement of studies in sections based on their respective focus e.g. education, lung function, models of care, novel monitoring devices etc. We note that this was the case for studies of electronic adherence monitoring.	Thank you for your comment. Tele-healthcare is an evolving area and the approach you suggest may be possible in future guidance.
Novartis Pharmaceuticals UK Ltd	Short	12/13	Comment on table 2 and table 3 content	'Consider alternative diagnosis' should be changed to 'Consider alternative diagnoses' in these tables.	Thank you for your comment. This change has been made.

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Novartis Pharmaceuticals UK Ltd	Short	3	6	Chest tightness or chest problems should also be included in the list of asthma symptoms that people with suspected asthma should be checked for. This also aligns with the text in rows 6 and 7 on page 21 about asthma symptoms.	Thank you for your comment. The development process did not allow time for an evidence search on the value of every conceivable part of the clinical history. We agree that these questions are useful but since we did not look for evidence cannot explicitly recommend them.
Novartis Pharmaceuticals UK Ltd	Short	3	10	In this sentence we suggest adding in examples of the objective tests that should be conducted to diagnose asthma for clarity.	Thank you for your comment. NICE recommendations are as clear and concise as possible and it was felt that adding examples would unnecessarily lengthen the recommendation.
Novartis Pharmaceuticals UK Ltd	Short	3	20	We are uncertain that fractional exhaled nitric oxide testing will be available in many settings, particularly primary care.	Thank you for your comment. We agree this guideline calls for a change in practice, however there is evidence to show that asthma diagnosis needs to improve.
Novartis Pharmaceuticals UK Ltd	Short	4	23	In this sentence we suggest that for clarity a time frame is given for 'regular' e.g. every 6 months.	Thank you for your comment. This guidance is outside the scope of this guideline. The frequency of review should be determined for each patient depending on severity of illness and presence of factor associated with a higher risk of poor outcomes.
Novartis Pharmaceuticals UK Ltd	Short	5	21	We suggest that a definition for negative bronchodilator reversibility (BDR) is provided for clarity.	Thank you for your comment. This is provided in table 1 of the short version.
Novartis Pharmaceuticals UK Ltd	Short	10	5	Asthma can be a complex disease to diagnose therefore we believe that healthcare professionals should be made aware of the possibility of misdiagnosis and comorbidities. Therefore, we suggest adding information on these in the diagnosis and monitoring sections for clarity. In this section we also suggest adding in a statement that if diagnosis is inconclusive, consider referral to an asthma specialist.	Thank you for your comment. The potential alternative diagnosis and confounding comorbidities are outside the scope of this guideline. Re your last point, recommendation 1.3.20 says to consider alternative diagnoses or referral for second opinion in adults whose objective testing produces a mixed clinical picture.
Novartis Pharmaceuticals UK Ltd	Short	13	11/12	We suggest that 'other triggers' is stated as a bullet point on its own to not confuse occupational asthma and other triggers. Checking for avoidance of triggers in general is important in controlling asthma.	Thank you for your comment. This change has been made.
Novartis Pharmaceuticals UK Ltd	Short	14	17	We suggest adding a recommendation to this section stating that if asthma remains uncontrolled consider referral to an asthma specialist for review.	Thank you for your comment. In this guideline we have not looked at indications for referral, apart from when the initial diagnosis of asthma is in doubt.
Resuscitation Council (UK)	General			Thank you for the opportunity to see this draft guideline. It contains no elements that involve the activities or expertise of the Resuscitation Council (UK), so we have no comments to offer on this occasion.	Thank you for your comment.
Royal College of General Practitioners / Primary Care Respiratory Society UK				Re your questions 2. Would implementation of any of the draft recommendations have significant cost implications? 3. What would help users overcome any challenges? We have significant concerns about: a. The cost of spirometry training and certification – these are only just becoming clear now that the assessment and certification process is underway. b. The cost of purchasing and using FeNO c. The costs of increased referral to secondary care services for asthma diagnosis. We think there is a significant risk of a substantial increase in such referrals potentially delaying diagnosis and delaying access to specialist paediatric and respiratory services for those who most need them, and incurring increased costs. This is not raised in the draft guideline at all and should be.	Thank you for your comment. Firstly, the NHS England guidance for quality-assured spirometry is nationally adopted and will raise standards in diagnostic spirometry. This initiative is independent of NICE. Whilst we acknowledge there will be initial upfront costs to be met, this NICE guideline will improve patient outcomes and is cost-effective to the NHS in the long-term; NICE's cost impact assessment projects a saving of approximately £14 million per year in England, before implementation costs. This has now been emphasised in the guideline introduction. The Guideline Committee (GC) acknowledge that the expected cost savings in unnecessary drug treatment for asthma (through more accurate diagnoses) will be realised at the CCG-level, and not by individual GP practices. It is outside the GC's remit to recommend how services should be organised; however, the GC would expect that CCGs would support individual GP practices to implement the guideline e.g. purchase of FeNO machines, to achieve cost savings through economies of scale. This view is reflected in recommendation 1.3.1 on diagnostic hubs. The wording of this recommendation has been changed to make it clearer that it is aimed at clinical commissioning groups. GPs use diagnostic hubs or hospital services for other investigations, so it is not unreasonable to suggest the same for asthma tests. The GC acknowledges that currently access to bronchial challenge tests is limited and have made a recommendation on what to do if a bronchial challenge test is not available. However, bronchial challenge is

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				Comments from clinicians following articles in medical journals on the draft guideline confirm this view. d. Lack of provision of bronchial challenge testing in secondary care. e. The Markov model for determining costs and health outcomes (Figure 312: page 632) assumes that false negatives will be corrected, as 'after an exacerbation the patient will be correctly re- diagnosed as having asthma'. The occurrence of exacerbations is the hall-mark of asthma, and many people with asthma will have a documented history of an exacerbation (ideally confirmed with peak flow variability) at the beginning of the diagnostic pathway. Should this not be the first (no cost) step in making the diagnosis enabling the potentially costly investigations to be applied to those in whom there is no such confirmed history? Overcoming challenges: • Diagnostic hubs may work in some places but will not suit all • Commissioners need to consider how they will address cost of spirometry training, and cost of FeNO whatever model is adopted. A specific recommendation explicitly addressed to commissioners would be helpful. • The guideline also needs to highlight the potential for increased referrals to secondary care to commissioners and acute centres, so that capacity issues can be planned for.	the single most accurate diagnostic test for asthma and the GC has tried to limit its use to those patients who need it most. Recommending it in this guideline will hopefully drive the necessary change in service provision. GCWe believe that it is more common for people to present with less severe symptoms than with an acute exacerbation, and the guideline is therefore tailored mainly to this commonest situation. If patients do present in an exacerbation we agree that tests could be done, if possible, at that time, as we have indicated in Recommendation 1.1.5. This might include making serial peak flow measurements. Whilst we also agree that many people with asthma will have a documented history of an exacerbation, we do not agree that this applies to those with undiagnosed asthma, and it is the undiagnosed to whom the diagnosis section of this guideline should be applied. The GC acknowledge that at first the number of referrals to secondary care may increase whilst provision of services is established in primary care. However, in the medium to long term, the GC envisage that diagnosis is made in the community setting.
Royal College of General Practitioners / Primary Care Respiratory Society UK				Substantial issues over implementation remain of concern to us: FeNO testing is available in very few practices and carries significant costs – both for purchase of the equipment and ongoing use of consumables. No funding has been identified to make FeNO testing more widely available – the guideline leaves this matter to commissioners. One of the pilot practices purchased the equipment and used it during the pilot but will not now fund its ongoing use on the basis of excessive cost. There are major training needs if quality assured diagnostic spirometry is to be widely available in primary care. We fully support moves to improve the quality of diagnostic spirometry but are aware of the challenges and the need for funding in achieving this. The current recommendations for certification in spirometry in primary care will only come into full force in 2021. Spirometry testing is in any case normal in the majority of patients with asthma diagnosed in primary care, as the pilot confirmed. There are thus significant concerns over the implementation of this guideline in practice. It would be helpful if NICE were to consider the evidence from implementation studies in which different diagnostic algorithms have been evaluated.	Thank you for your comment. Please see responses above to very similar points made here including the issue of cost. In addition, we note that spirometry has long been recommended as part of the diagnostic work-up for asthma in the BTS/SIGN guideline. Although spirometry most commonly produced non-obstructive values in the feasibility study, obstructive airways disease was demonstrated in a significant minority. NICE guidelines on other conditions are published without initial testing. This guideline on asthma has gone a step further and piloted the algorithms for 6 months and demonstrated that they are implementable.
Royal College of General Practitioners / Primary Care				We said in our 2015 comments : • 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	Thank you for your comment. Our response to your 2015 comments is below and has also been published in the 2015 Stakeholder comments table.: 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

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Respiratory Society UK				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. We remain of this view.	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 B & 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. We remain of this view, although we note that in the updated 2016 version of the BTS/SIGN guideline the Grade C recommendation has been removed.
Royal College of General Practitioners / Primary Care Respiratory Society UK				We remain concerned over major points of discrepancy between this guideline and the existing NICE- accredited BTS-SIGN British Asthma Guideline. We think that the existence of conflicting advice in different evidence based UK guidelines is a problem in and of itself. We have requested that NICE highlights and explains areas of discrepancy but this appears not to have been done.	Thank you for your comment. The GC acknowledges that there are differences in the remits and methodologies used by both NICE and BTS/SIGN. For example, NICE uses GRADE methodology and considers cost-effectiveness evidence. Notwithstanding this, the GC considers the recommendations in both guidelines are broadly similar. The main difference between the BTS/SIGN guideline and NICE guideline is that the BTS/SIGN guideline permits no objective testing if the clinician is convinced of an asthma diagnosis on clinical history, whereas the NICE guideline recommends objective testing in all cases. NICE and BTS/SIGN are considering how best to clarify advice for those aspects of asthma care not covered by the NICE pathway for asthma diagnosis and management. NICE and BTS/SIGN are also discussing a longer term solution and how we might bring the two guidelines together.
Royal College of General Practitioners / Primary Care Respiratory Society UK				We hope that NICE will take these matters into consideration in its final decision on whether to issue this guideline and in the final version of the guideline if it is issued. It is not clear that the feasibility testing has achieved any greater understanding of how this guideline should be implemented in practice, nor resulted in any advice on how to address the practical challenges of implementation. The setting up of diagnostic hubs has been suggested but no evidence presented for this suggestion, and such hubs will not be appropriate everywhere. We believe that the recommended approach to asthma diagnosis outlined in the draft guideline should be further piloted and not mandated.	Thank you for your comment. The GC considered that the results of the feasibility project were positive and demonstrated that the algorithms are implementable. The GC acknowledges that the recommendation on diagnostic hubs is not based on an evidence review. The GC believes that the guideline is implementable and cost savings could be achieved through economies of scale if CCGs facilitated implementation. The NICE adoption team are planning to develop a web based adoption support resource which shares learning from the sites involved in the feasibility study to support those in practice responsible for implementing this guideline.
Royal College of General Practitioners / Primary Care Respiratory Society UK				Both the RCGP and PCRS-UK still have severe reservations about the draft guideline and especially about the confusion that will result with advice given by the BTS/SIGN guidance. It is vital that a consensus is reached between NICE and BTS/SIGN to avoid confusion which can only be to the detriment of the care of people with asthma The view of PCRS UK is, given the problems identified below, that it would be preferable that this guideline was not published.	Thank you for your comment. The GC acknowledges that there are differences in the remits and methodologies used by both NICE and BTS/SIGN. For example, NICE uses GRADE methodology and considers cost-effectiveness evidence. Notwithstanding this, the GC considers the recommendations in both guidelines are broadly similar. The main difference between the BTS/SIGN guideline and NICE guideline is that the BTS/SIGN guideline permits no objective testing if the clinician is convinced of an asthma diagnosis on clinical history, whereas the NICE guideline recommends objective testing in all cases.
Royal College of General Practitioners / Primary Care Respiratory Society UK				The Primary Care Respiratory Society UK (PCRS-UK) and RCGP share the concern over the significant issue of asthma misdiagnosis suggested by the studies quoted in the draft guideline. The PCRS-UK has an active campaign on improving diagnosis of respiratory problems in primary care and education in improved diagnostic practice is a key element in Primary Care Respiratory Academy program. The PCRS-UK has been an active participant in the move to create a National register for spirometry, and contributed to the creation of commissioning guidance on spirometry, which is yet to be published. The PCRS-UK believes that there is major scope for improvement with better use of well established diagnostic approaches by well trained clinicians.	Thank you for your comment. The GC agrees there is a problem with misdiagnosis of asthma and hope your education programme is successful in helping to reduce this.

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Royal College of General Practitioners / Primary Care Respiratory Society UK				The RCGP and PCRS-UK are disappointed that this draft guideline has been reissued for consultation with minimal changes from the draft, which appeared in 2015. It is not clear that the significant concerns about implementation borne out by the field testing have resulted in any significant change to the first draft guideline. The PCRS-UK and RCGP submitted extensive comments on the initial draft and expressed major concerns about the feasibility of implementation. The RCGP and PCRS-UK comments from March 2015 are attached at the end of this document (shaded in grey) for reference. The RCGP and PCRS-UK are of the opinion that these comments remain valid and would request that these comments should be reconsidered.	Thank you for your comment. The feasibility project demonstrated that the algorithms were implementable (appendix Q). Furthermore, there has been no new evidence published in the intervening period that would warrant a change in recommendations (appendix R). Therefore, the draft guideline has been reissued for consultation with changes in the presentation of the algorithms for clarity and simplicity, and additional recommendations around what to do with people at initial presentation and if access to bronchial challenge tests is limited. The GC's remit was to produce a clinical and cost-effective guideline on the diagnosis and monitoring of asthma, which the GC has fulfilled. Whilst we acknowledge there will be initial upfront costs to be met, if implemented, the guideline will improve patient outcomes and is cost-effective to the NHS in the long-term; NICE's cost impact assessment projects a saving of approximately £14 million per year in England, before implementation costs. This has now been emphasised in the guideline introduction. The GC acknowledge that the expected cost savings in unnecessary drug treatment for asthma (through more accurate diagnoses) will be realised at the CCG-level, and not by individual GP practices. It is outside of the GC's remit to recommend how services should be organised; however, the GC would expect that CCGs would support individual GP practices to implement the guideline e.g. purchase of FeNO machines, to achieve cost savings through economies of scale. This view is reflected in recommendation 1.3.1 on diagnostic hubs. The wording of this recommendation has been changed to make it clearer who the recommendation is aimed at. GPs use diagnostic hubs or hospital services for other investigations, so it is not unreasonable to suggest the same for asthma tests. The GC's responses to your comments from 2015 are copied below (shaded in grey) and we stand by the original response.
Royal College of General Practitioners / Primary Care Respiratory Society UK				In the light of the concerns expressed by both organisations and others over the feasibility of implementing this guideline, publication was commendably paused and a pilot study of guideline implementation was undertaken. A report from that pilot study appears as an appendix to the current draft. This study included 143 patients with suspected asthma and 35 patients diagnosed with asthma in the seven participating practices. These highly motivated practices were provided with FeNO testing at no cost, and financial support for spirometry training for staff (which practices had difficulty in accessing). In this study – • 59% of patients with suspected asthma remained of uncertain diagnostic status at the end of the study period (25% had asthma). • Spirometry was normal in 73 % of those diagnosed with asthma. • Diagnostic value of FeNO in the study is not reported. • Fourteen (10%) of the patients with suspected asthma reached the point in the algorithm of requiring bronchial provocation testing – which was in effect not available – no patient had undergone this test by the time the project closed. The report states that six of the seven practices would continue to use the diagnostic algorithm if the guideline is issued. We attended the meeting in December 2016 at which the pilot practices reported back and came away with an impression of greater doubt over this, particularly if practices were required to fund FeNO testing and spirometry training themselves. In our view the experience in the pilots has amply borne out a number of our	Thank you for your comment. However, we believe you have an incorrect interpretation of the feasibility project report. The feasibility study reflected real life implementation of a clinical guideline where patient factors and clinical judgement influence the final action for each individual patient. Only 10 people were unable to complete the diagnostic tests. Of the 52 people where there were deviations from the algorithm these were commonly where practitioners completed an additional test or peak flow measurements were missed. Practices did not highlight these as implementation issues. The study used the diagnostic values for FeNO recommended in the NICE guideline The GC acknowledges that currently access to bronchial challenge tests is limited and has made a recommendation on what to do if a bronchial challenge test is not available. However, bronchial challenge is the single most accurate diagnostic test for asthma. The GC has tried to limit it to those patients who need it most. Recommending it in this guideline will hopefully drive the necessary change in service provision.

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				concerns. We disagree with the conclusion in the feasibility study that the algorithm works in general practice as in only 54.7% people with suspected asthma were able to conform to the algorithm. (para 19 page 853. Appendix Q) i.e. in almost 1 in 2 it didn't work. It appears that NICE has selectively ignored aspects of the experience of the feasibility testing sites, which would prevent them from publishing this guidance virtually unchanged from its original draft from 2015.	The feasibility report, which has been agreed by all the participating sites, concludes that: • All sites agreed that the algorithm could be implemented into primary care as it stands, and that implementation is not an overwhelming burden for those patients who were already being referred appropriately for spirometry assessment by the practice nurse. • Of the 7 sites, 6 said they would like to continue with the algorithm if it remained unchanged at publication. However all sites stated that this was helped by being given the FeNO device free of charge by the manufacturer.
Royal College of General Practitioners / Primary Care Respiratory Society UK	Full guideline	134 144	13 17	FeNO may well have an important role in asthma diagnosis but we do not believe that the evidence currently warrants mandating its use in the majority of cases, and, as discussed above there are serious issues of implementation in doing this now. It is difficult to understand how NICE is able to recommend such a central position for FeNO in asthma diagnosis and at the same time state: '*However, as FeNO is a relatively new diagnostic tool the diagnostic test accuracy is currently uncertain.*' Furthermore, it appears that there is a paucity of economic evidence for FeNO, which is relevant since the field testing identified that cost of FeNO was a significant barrier. '*No relevant economic evaluations were identified*'. We also note the following from the 2017 update to the global GINA asthma guideline http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/ Page 20 *FENO has not been established as useful for ruling or ruling out a diagnosis of asthma, as defined on p.14. FENO is higher in eosinophilic asthma but also in non-asthma conditions (e.g. eosinophilic bronchitis, atopy, allergic rhinitis, eczema), and it is not elevated in some asthma phenotypes (e.g. neutrophilic asthma). Several other factors affect FENO levels:26 it is lower in smokers and is decreased during bronchoconstriction and in the early phases of allergic response;27 it may be increased or decreased during viral respiratory infections26* These statements from the GINA guideline suggest that the evidence for the routine inclusion of FeNO measurement in asthma diagnosis is not strong.	Thank you for your comment. You quote a sentence from the introduction to the FeNO section which simply explains why the GC needed to look at the evidence. Having seen the evidence they conclude that this is a useful test. It is not perfect, but has better diagnostic accuracy than bronchodilator reversibility or PEF variability which are currently in use. Regarding your comment re paucity of economic evidence, although no economic evidence was included from other authors in this guideline for FeNO diagnosis, an original economic evaluation was conducted. This analysis is informed by several systematic reviews and produces robust conclusions. Therefore it is highly unlikely additional economic studies would change the conclusions. We agree, this speaks to using FeNO in isolation to diagnose asthma. We use it as part of a diagnostic algorithm

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Royal College of General Practitioners / Primary Care Respiratory Society UK	Short version			Since there are significant issues around implementation of the guideline, it would be helpful for NICE to be specific about the issues commissioners need to address locally: lack of availability of FeNO in practices and many secondary care centres; lack of suitably trained spirometry operators and interpreters; lack of bronchial challenge testing in secondary care centres; the potential impact of increased referrals to specialist centres. NICE should highlight the need for research to develop a prediction rule for an asthma diagnosis, validate the rule (retrospectively and prospectively), before a cycle of implementation studies to understand, develop solutions to the barriers and then trial the diagnostic process in routine clinical care.	Thank you for your comment. Guidelines on other conditions are published without initial testing. This guideline on asthma has gone a step further and piloted the algorithms for 6 months and demonstrated that they are implementable. We agree that there will be challenges for commissioners but they will vary; for example, some centres do provide bronchial challenge testing currently.
Royal College of General Practitioners / Primary Care Respiratory Society UK				Please see our 2015 submission for more detailed comments. The summary points are repeated below - shaded in grey below.	Thank you for your comment.
Royal College of General Practitioners / Primary Care Respiratory Society UK				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. • 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. **Introductory Comments / An overview**	Thank you for your comment. Please see our response to your comment from 2015: 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 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 GC 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. However**,** a number of other stakeholders questioned the practicability of the suggested sequence of objective tests, and therefore a feasibility study will be performed to evaluate these concerns. 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 B & 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.

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				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 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 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 GC.	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 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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				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.** 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 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	

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				which, by requiring ARTP equivalent training and recertification for those performing and interpreting 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. **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 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	

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				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 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 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.**	

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				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 was attached.	
Royal College of General Practitioners / Primary Care Respiratory Society UK	Short guideline	3	3	Good history taking importantly involves asking about previous respiratory illnesses, treatments and response to treatments – including treatments given in the past for wheezing. This recommendation is not explicitly included and should be.	Thank you for your comment. This guideline is designed to be used at the first presentation with respiratory symptoms. The development process did not allow time for an evidence search on the value of every conceivable part of the clinical history. We agree that these questions are useful but since we did not look for evidence cannot explicitly recommend them.
Royal College of General Practitioners / Primary Care Respiratory Society UK	Short version	5	7	The guideline does now suggest that diagnostic hubs may be necessary to achieve economies of scale: while this may be a sensible approach in some settings, it will not be appropriate everywhere. There does not appear to be any evidence base for this recommendation. A guideline that would depend for its implementation on a rapid and widespread provision of new community based services at a time of unprecedented financial constraint is unwise. It would be a major and expensive change in the nature of health service provision in the UK to propose a system in which the diagnosis of common chronic conditions cannot be made in primary care without the creation of a new diagnostic service and referral process. Furthermore, the creation of diagnostic hubs may lead to a deskilling of practices in performing and interpreting spirometry, so that the monitoring of respiratory conditions could be adversely affected.	Thank you for your comment. The GC acknowledges that the recommendation on diagnostic hubs is not based on an evidence review. The size and location of hubs is not specified, and in some instances might easily consist of a few practices combining in order that each one does not have to have an ARTP-certified practitioner to perform spirometry, etc, problems you have pointed out yourselves in other comments. Having spirometry performed outside the practice would not need to cause deskilling in interpreting the results which could be presented back to the relevant GP.
Royal College of General Practitioners / Primary Care Respiratory Society UK	Short	6 5	2 14,17	The draft guideline continues to recommend spirometry in all patients capable of performing this test and FeNO measurement in all adults and some children in order for a diagnosis of asthma to be made. For example algorithm B for children/young people recommends spirometry ahead of FeNO as a diagnostic test. There is only one study of spirometry in children (para 18, page 118) which is of low quality and does not look at the utility of the ratio of Fev-1/FVC but merely that the Fev-1< 80% can be an indicator of asthma . There are no studies (page 104 para 11) looking at the utility of reversibility testing in children. It is really difficult to see why, in an evidence -based guideline, spirometry testing has been recommended in children. Conversely FeNO testing shows relatively high sensitivity and specificity in medium to high quality studies in children. We remain of the belief that the evidence base for these interventions and their positioning in the algorithms does not support the recommendations.	Thank you for your comment. We agree that spirometry is not the most sensitive test for asthma, hence a diagnosis of asthma should not be made on the basis of a spirometry test alone. And since the presence of bronchodilator reversibility is a hallmark of asthma, the GC consider spirometry is a useful test and it would be wrong to omit it. It is a recommended test for children in whom it can be measured in the BTS/SIGN guideline so it is not a change in practice.
Royal College of General Practitioners / Primary	Short version	6	15	Peak flow monitoring for the diagnosis of asthma is a cheap and widely available technique already extensively used in primary care. It has a high specificity – desirable if the concern is to avoid over-diagnosis. Its validity is accepted by the GC since it is incorporated in the algorithms for clarification in cases of doubt. It is particularly	Thank you for your comment. The GC did not consider this test showed sufficient diagnostic accuracy to warrant recommending it first-line. The utility of peak flow variability has been assessed and positioned in the algorithm. However, there is nothing to stop clinicians providing this test at the same time as spirometry and FeNO.

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Care Respiratory Society UK				likely to pick up significant variability – and is more likely to be complied with – if introduced at first presentation when the patient is symptomatic and before or at the time of commencement of treatment. It should be recommended as a first line objective test of airways obstruction.	
Royal College of General Practitioners / Primary Care Respiratory Society UK	Short Guideline Full guideline	13 119	13	It is regrettable that use of the RCP 3 questions in monitoring asthma control has been discarded due to lack of RCTs. When the utility of skin prick testing in diagnosis was considered then cross sectional and observational studies were included (Page 119) NICE itself commissioned a validation study of the RCP 3 questions, Pinnock et al PCRJ 2012 288-294. which showed that the RCP 3 questions had good cross sectional and longitudinal validity in terms of monitoring asthma control.	Thank you for your comment. In this instance there were plenty of randomised trials to consider, and it was not necessary to go to lower level evidence.
Royal College of General Practitioners / Primary Care Respiratory Society UK	Short guideline	15		The algorithm on initial clinical assessment (Algorithm A) does now say " Treat people immediately if they are acutely unwell on presentation" This is of course, a trial of treatment. " If possible perform objective tests (including FeNo and spirometry) at the time of presentation." This recommendation will very rarely if ever, be possible . What absolutely is possible, and should be recommended in the guideline, is peak flow measurement – and the commencement of a period of peak flow monitoring to collect this important evidence of response to treatment.	Thank you for your comment. This is a pragmatic recommendation made for reasons of patient safety. We agree that PEF measurements might also be useful in this context, although it represents a minority of new presentations.
Royal College of General Practitioners / Primary Care Respiratory Society UK	Short version Appendices	16 849 850	1 8 5	Spirometry with reversibility testing, may be desirable where quality assured spirometry is available in a timely manner, but this may not always be the case - and even in the pilot practices, this test was normal in the majority of patients diagnosed with asthma. (73%) The evidence base for using spirometry and reversibility in children is very weak, as we pointed out in our earlier comments. We cannot understand why spirometry testing has been recommended in children.	Thank you for your comment. The GC considers that a significant minority of people (27% in the feasibility study) with asthma have obstructive spirometry, and its presence allows reversibility testing. The guidance for children covers those up to the age of 16, and spirometry can be done more easily as the child grows older. Airflow obstruction is a fundamental abnormality in asthma and the GC believes it is as important to identify it in children as in adults.
Royal College of General Practitioners / Primary Care Respiratory Society UK	Short	18	2	It seems perverse to us that the respiratory community is not being consulted over implementation guidance.	Thank you for your comment. This section is standard text and is included in all guidelines. The adoption team are developing an adoption resource to be published on the NICE website after guideline publication. The resource will be in line with the guideline and stakeholders will be contacted for comment.
Royal College of Nursing	General	General	General	The Royal College of Nursing invited members who care for people with respiratory conditions to review the draft document on its behalf.	Thank you for your comment.

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				The comments below include the views of our members.	
Royal College of Nursing	Full	General	General	The document is very detailed, complex and difficult to read in some parts and could potentially lead to healthcare professionals missing key elements of the guidelines.	Thank you for your comment. NICE produces a short version of the guideline which only contains the recommendations. NICE recommendations are written in plain English. We have also produced algorithms which summarise the diagnostic pathway in visual form. The NICE Implementation team will also produce implementation tools to facilitate uptake of the guideline. The GC acknowledges that diagnosis of a complex variable disease can be complex.
Royal College of Nursing	Full	General	General	It can take longer than anticipated when performing spirometry and FeNO tests with young children; depending on several factors including age, cognitive development, mood etc. this could increase cost. In primary care not all practitioners are used to getting children to perform tests for them.	Thank you for your comment. We agree that performing tests in this age group can be more challenging than in adults, but this is true of tests for other conditions, not just asthma; it doesn't mean the tests should not be done. The GC has made specific recommendations in children and young people around what to do if they cannot perform the tests at that point in time.
Royal College of Nursing	Full	General	General	One reviewer considered that some of the clinical evidence cited in the guideline, particularly that relating to children, seem to be of low quality. We suggest that this is addressed in a future update.	Thank you for your comment. We agree that the evidence base for children and young people was either lacking or of low quality; hence the GC made a high-priority research recommendation on asthma diagnosis in children and young people. We hope that high quality studies on this topic will be conducted to inform future updates of the guideline.
Royal College of Nursing	Full	General	General	To properly follow all these recommendations for an asthma review could be time consuming. Asthma review appointments should be longer…has implications for primary care. Also who does this, GP or practice nurse? Many nurses lead on respiratory management especially with advanced level nurse practice development. General practice nurses often cover the age spectrum and training is essential especially with new spirometry guidance to ensure quality and safety.	Thank you for your comment. We agree that the guideline recommends doing more tests and some changes in primary care organisation and training will be needed to facilitate this. Whilst we acknowledge there will be initial upfront costs to be met, if implemented, the guideline will improve patient outcomes and is cost-effective to the NHS in the long-term; NICE's cost impact assessment projects a saving of approximately £14 million per year in England, before implementation costs.
Royal College of Nursing	Full	General	General	We are concerned that having more than one national guideline from different organisations will lead to confusion especially when they can contradict e.g. British Thoracic Society (BTS) guidance which is currently widely used. It is essential that there is sufficient funding to implement these NICE guidelines in an equitable and robust manner.	Thank you for your comment. The GC acknowledges that there are differences in the remits and methodologies used by NICE and BTS/SIGN and this has resulted in some differences in the guidance offered. Although we agree that the BTS/SIGN guideline is widely used in the UK, we do not think that its diagnostic recommendations are implemented as widely as its treatment recommendations. NICE and BTS/SIGN are considering how best to clarify advice for those aspects of asthma care not covered by the NICE pathway for asthma diagnosis and management. NICE and BTS/SIGN are also discussing a longer term solution and how we might bring the two guidelines together.
Royal College of Paediatrics and Child Health	General	-	-	This is a very useful document	Thank you for your comment.
Royal College of Paediatrics and Child Health		General		Overall the guidelines are clearly written and any evidence-based approach to the diagnosis and monitoring of asthma in children and young people is most welcome. Worth noting that BPRS members have mainly considered aspects relevant to children and young people only. Below is a summation of comments received from BPRS members.	Thank you for your comment.
Royal College of Paediatrics and Child Health		General		From secondary care (DGH) point of view: increased use of spirometry and FeNO measurements will impact on resource requirements and training considerably if needed for every child with ?asthma. At a primary care level this is certainly not practical within most current set ups and will increase workloads even in tertiary care	Thank you for your comment. The GC believes that economies of scale can be generated by diagnostic hubs. We agree that the guideline recommends doing more tests. We hope that primary care will invest in FeNO, so that it can be used without requiring referral referred into secondary care . FeNO is relatively new to both secondary care and primary care, but it has been shown to be a useful test in the GC's appraisal of the evidence.

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				physiology labs too. (Please also see specific comment below re. 1.1.2 and 1.2.1 Spirometry is often challenging logistically and physically when children are acutely unwell – has this been considered?	Please note, the guidance suggests measuring objective tests **if possible** when children (or adults) present acutely unwell.
Royal College of Paediatrics and Child Health		General		Did the scope extend to recommendations re. which FeNO metres are recommended?	Thank you for your comment. No the scope did not include a comparison of one FeNO meter with another. The issue was not raised by stakeholders at consultation on the scope. We note that all FeNO meters will have to meet statutory requirements for Medical Devices.
Royal College of Paediatrics and Child Health	Full version	General		Objective testing for asthma is a good thing and pleased that this has been retained. We can all acknowledge that there is a lack of a gold standard test for the diagnosis of asthma and therefore using multiple objective measures as recommended by this guideline is a good thing. However, the algorithms are too didactic. There is likely to be a delay between initial presentation and an appointment for testing (the pilot centres booked up to 1 hour appointments for diagnostic tests and therefore there was usually a delay of about 2 weeks). This is an opportunity to carry out PEF testing in this time and therefore when the patient attends for spirometry and FENO testing these PEFv results will be available too and all 3 tests can be looked at at one appointment rather than sending the patient away again if they do not fulfil the criteria for asthma based on FEV1/FVC, BDR or FENO and asking them then to do PEF measurements and coming back for another appointments. Also, its unclear why it takes 10mins to do a PEF in primary care (and then 10mins to interpret the results) but only 5 -10mins for FENO and 8 – 17mins for BDR.	Thank you for your comment. The GC did not consider that PEF variability showed sufficient diagnostic accuracy to warrant recommending it first-line. The utility of peak flow variability has been assessed and positioned in the algorithm. However, there is nothing to stop clinicians providing this test at the same time as spirometry and FeNO. Regarding your query about time required to do each test, the GC feel that 5-10 minutes for PEF variability is appropriate since the patient has to be instructed how to make the measurements and how to record them. The patient then returns with their PEF record and this needs to be assessed. For FeNO a measurement is produced 1 minute after the manoeuvre has been done.
Royal College of Paediatrics and Child Health	Full version	General		The continued inclusion of AHR testing in the adult algorithm is problematic and currently this is only available in secondary / tertiary care. The data for the economic analysis of AHR testing is presented in a different way to the other tests. It would seem better for the more simple paediatric algorithm to be used for all age groups.	Thank you for your comment. The GC acknowledges that currently access to bronchial challenge tests is limited and have made a recommendation on what to do if a bronchial challenge test is not available. However, bronchial challenge is the single most accurate diagnostic test for asthma. The GC has tried to limit it to those patients who need it most. Recommending it in this guideline will hopefully drive the necessary change in service provision.
Royal College of Paediatrics and Child Health	Full version	General		It is disappointing that the advice of the ARTP has been ignored and FEV1/FVC <70% is still the recommended cut point for airway obstruction rather than LLN.	Thank you for your comment. We agree that LLN should be used if available. We have included it in an amended recommendation.
Royal College of Paediatrics and Child Health	Full version	General		The data on diagnostic tests would be better presented as positive and negative predictive values rather than sensitivity and specificity, particularly as many of the studies are assessing the utility of a test in those with a diagnosis of asthma and hence the pre-test probability is high.	Thank you for your comment. We focus on sensitivity and specificity for decision making and recommendations because they are intrinsic to the test. PPV and NPV are influenced by the prevalence of the target condition and therefore, are only accurate for a population with similar prevalence to the population tested. Consequently, it is necessary to consider the prevalence when interpreting PPV and NPV. Also, study populations are rarely drawn from the same population pool and may therefore have a different disease prevalence. This makes it difficult to compare studies appropriately when using PPV and NPV.
Royal College of Paediatrics and Child Health	Short version	4	5	1.1.6 Please can the guideline clarify whether exercise testing in under 17 year olds is recommended?	Thank you for your comment. Exercise challenge test could be offered to under 17s based on the review of evidence, hence the wording of this recommendation; the evidence showed that this test was not clinically and cost effective in adults given the availability of better tests in this population group, therefore the GC made a 'Do not' recommendation in adults. But there was no evidence to suggest that it should not be done in children.

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Royal College of Paediatrics and Child Health	Short version	5	8	1.3.1 Really like the idea of a diagnostic hub. Ideally the hubs will be able to complete testing in all age ranges within one month of referral.	Thank you for your comment.
Royal College of Paediatrics and Child Health	Short version	5	17	1.3.3 FeNO >=35ppb is not an unreasonable threshold, likely to be specific but on a thin evidence base.	Thank you for your comment. We agree.
Royal College of Paediatrics and Child Health	Short version	6	3	1.3.5 The guideline might point out that very few children will be expected to have an FEV1/FVC ratio of <70%	Thank you for your comment. Please see the footnote. We have now added reference to use of the LLN.
Royal College of Paediatrics and Child Health	Short version	3+4	10+22	1.1.2 There is agreement with the aim of statement 1.2.1 (i.e. to introduce objective testing into the diagnostic process) but is it ethical to withhold asthma treatment (i.e. inhaled corticosteroids) which will improve asthma control and reduce the risk of asthma attacks until testing is complete when the clinician is confident that the diagnosis is asthma? Inhaled corticosteroid treatment at prescribed doses has an excellent safety profile and a wide therapeutic index. If it is acceptable to use clinical judgement to guide treatment choice in a four year old (1.2.1), why is it not acceptable to use the same judgement in a 5 year old?	Thank you for your comment. We make it clear in rec 1.1.5 that you treat people who are acutely unwell. We have added a recommendation saying to tell patients to come back if they become unwell whilst waiting for objective tests. For most people it is better to wait for tests before embarking on a lifetime of medication.
Royal College of Paediatrics and Child Health	Short version	8	9	1.3.14. Many children with symptoms suggestive of asthma will have either FeNO>=35 or positive peak flow variability. Suspect that very few children will have obstructive spirometry so the presence of positive bronchodilator reversibility is unlikely to be relevant since this latter phenomenon has to coexist with obstructive spirometry. The very reasonable aim of this guideline is to ensure that at least one objective test is abnormal and would suggest that NICE stick to having an abnormality on one of the four tests as sufficient supportive evidence to proceed to give a trial of inhaled corticosteroid medication. Would also like the guideline to make it clear that a trial of inhaled corticosteroid medication can be started based on symptoms alone even if testing is all normal as long as there is a 2 month review of symptoms.	Thank you for your comment. Spirometry is obstructed in a significant minority of patients with asthma and has long been recommended, where possible, in the BTS/SIGN guideline. PEF variability also shows poor sensitivity. The concept of treating children without an absolutely clear diagnosis is already captured in recommendation 1.3.15 (re-numbered from 1.3.14 after consultation amendments) which suggests starting treatment and reviewing when only one test is abnormal. The GC believe that treating for asthma when all tests are normal is not advisable, and that other causes of the symptoms should be considered – see recommendation 1.3.17
Royal College of Paediatrics and Child Health	Short version	9	1	1.3.17. Which evidence this is based on? Also suspect that hospital services are not able to cope with the extra burden of work this statement might deliver. Would suggest that a referral in this situation would be appropriate if a two month trial of inhaled steroid treatment is negative.	Thank you for your comment. This recommendation is about referring children who are still unwell but their objective test results do not suggest asthma. It is far less likely that a child will respond to inhaled steroids if FeNO is negative, so your suggestion will delay a positive diagnosis.
Royal College of Paediatrics and Child Health	Short version	10	1-12	1.3.10 Peak flow variability Page 10 lines 1-12. The text explaining the algorithms could come in section 1.1. Currently Algorithm A is not referred to at all and "Algorithm B" is the first mention of any algorithm (section 1.2.1 and also on Page 8 or 25, line 8).	Thank you for your comment. We agree and have added reference to algorithm A in the recommendations on initial clinical assessment.
Royal College of Paediatrics	Short version	10	6	1.3.21. This is a valid practice point to aspire to but for the points made previously, this point will be difficult to achieve in paediatric practice in the real-world.	Thank you for your comment. We agree that performing tests in this age group can be more challenging than in adults, but this is true of tests for other conditions, not just asthma; it doesn't mean the tests should not be

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and Child Health					done. The GC has made specific recommendations in children and young people around what to do if they cannot perform the tests at that point in time.
Royal College of Paediatrics and Child Health	Short version	11	1	Table 1. Please clarify that the guideline does not recommend methacholine testing in children and young people.	Thank you for your comment. You are correct; table 1 has been amended to reflect this.
Royal College of Paediatrics and Child Health	Short version	14	1	1.5.3. Spirometry and peak flow variability are poorly correlated to asthma control. What is a significant change in spirometry and leak flow variability and what should the clinician do if there is a significant change?	Thank you for your comment. We measure spirometry as part of the diagnostic process but management will be left to the individual clinician. A sensible clinician would look at adherence, especially if there is significant reversibility, review the level of medication and/or consider referral to a specialist. Both tests have a degree of variability and the results should be considered in conjunction with clinical symptoms before making management decisions. The GC is unable to give guidance on a specific cut-off figure.
Royal College of Paediatrics and Child Health	Full version	40		4.1 The diagnostic algorithms are a little clearer from previous versions (clinically that is, the formatting is terrible) as much of the text has been removed. The addition of the box in algorithm 4.1 advising to treat people immediately if acutely unwell is welcomed. However, as this is now included it makes no sense that treatment response (measured objectively) is not included anywhere in the algorithm.	Thank you for your comment. Bronchodilator reversibility in the presence of obstructive spirometry is embedded within the algorithm, and this applies if performed at an acute presentation.
Teva UK Limited	Full	general	general	We welcome the opportunity to comment on this consultation. Teva UK Limited are in agreement with the details in the document from our perspective and in particular the focus on adherence and inhaler technique. We welcome further engagement in the process as this proceeds to finalisation.	Thank you for your comment.
The Assocation of Respiratory Nurse Specialists	Full	43	18	Is it appropriate to suggest performing objective tests such as FENo and in particular spirometry on someone having an acute asthma attack? For most people clinical judgement would prevent this, but there are always those who perhaps may not understand the speed in which an asthma attack can develop.	Thank you for your comment. NICE clinical guidelines do not replace clinical judgment. It is possible to perform spirometry acutely in some circumstances, including that the attack is not too severe. The recommendation has been re-worded: .1.5 Treat people immediately if they are acutely unwell at presentation. If the equipment is available and testing will not compromise treatment of the acute episode,possible, perform objective tests (including fractional exhaled nitric oxide [FeNO], spirometry and peak flow variability) at the time of presentation. If objective tests cannot be done immediately, they should be done when acute symptoms have been controlled, but advise patients to contact the practice immediately if they become unwell while waiting to have objective tests.
The Association of Respiratory Nurse Specialists	Appendices A-R document		General	Whilst these appendices will be interesting to some, the vast majority of people that may utilise the main set of guidance will find no day to day benefit from them and many will expect useful diagrams which are present within the main guidance and the short version.	Thank you for your comment. The algorithms will be made available as a separate resource as well as in the Full Guideline.
The Association of Respiratory Nurse Specialists	Full		General	Whilst ARNS are encouraged that NICE are looking to improve the diagnosis and monitoring of patients with asthma we have concerns about this guidance in terms of implementing it due to the financial burden several things within it may incur but in particular the FENo. Whilst we are not opposed to the principle, we feel that NICE have an obligation to ensure there is funding in place to support this form of testing on a wide scale basis be it in hubs or individual practices, as currently this does not happen in any setting. We are also concerned that advising the implementation of hubs may deskill many in diagnosing asthma and we feel that anyone who deals with	Thank you for your comment. The GC's remit was to produce a clinical and cost-effective guideline on the diagnosis and monitoring of asthma, which the GC has fulfilled. Whilst we acknowledge there will be initial upfront costs to be met, if implemented, the guideline will improve patient outcomes and is cost-effective to the NHS in the long-term; NICE's cost impact assessment projects a saving of approximately £14 million per year in England, before implementation costs. This has now been emphasised in the guideline introduction. The GC acknowledge that the expected cost savings in unnecessary drug treatment for asthma (through more accurate diagnoses) will be realised at the CCG-level, and not by individual GP practices. It is outside of the GC's remit to recommend how services should be organised; however, the GC would expect that CCGs would support individual GP practices to implement the guideline e.g. purchase of FeNO machines, to achieve cost savings through economies of scale. This view is reflected in recommendation 1.3.1 on diagnostic hubs. The wording of

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				asthma patients should have the ability to diagnose them. It is encouraging that several research questions have been flagged up. One of our other major concerns is the existence of two sets of national guidance, one from NICE and one from BTS/SIGN, with differing advice. This in itself is not conducive to good patient care and will lead to confusion. We urge the two organisations to work together to produce one definitive set of guidance, especially as NICE currently accredit the BTS/SIGN guidance.	this recommendation has been changed to make it clearer who the recommendation is aimed at. GPs use diagnostic hubs or hospital services for other conditions so it is not unreasonable to suggest that the same might be done for asthma tests. The GC acknowledges that there are differences in the remits and methodologies used by both NICE and BTS/SIGN and that this has resulted in some differences in the guidance offered.
The Association of Respiratory Nurse Specialists	Full	14	14	NICE have omitted to include tertiary centres in areas where these guidelines are applicable as not all people who attend them necessarily have severe or difficult to control asthma as per line 16.	Thank you for your comment. Most tertiary care centres also function as secondary care centres for their immediate locality and, as far as applying this guideline is concerned, they are therefore included.
The Association of Respiratory Nurse Specialists	Full	39	3	How often will NICE conduct a review to see if the guideline requires an update?	Thank you for your comment. NICE currently performs surveillance reviews every 2 years, although this frequency is under review and may change. Please see the NICE guidelines manual chapter 13 'Ensuring that published guidelines are current and accurate' at this link: https://www.nice.org.uk/process/pmg20/chapter/ensuring-that-published-guidelines-are-current-and-accurate
The Association of Respiratory Nurse Specialists	Full	41	General	You have stated in the algorithm to move onto peak flow monitoring if there is still diagnostic uncertainty. If however FENo testing is positive or negative of a diagnosis, your flow chart looks like you still have to do PEFR regardless.	Thank you for your comment. Yes you are correct.
The Association of Respiratory Nurse Specialists	Full	42	General	The same comment applies to the adult algorithm as above for the children's algorithm.	Thank you for your comment. Yes you are correct.
The Association of Respiratory Nurse Specialists	Full	44	16	There are concerns about the financial implications in recommending FENo for all adults and many children, as this will place a huge burden on budgets and so NICE need to consider supporting the rollout of these guidelines from the financial point of view or they will not be adhered to.	Thank you for your comment. Whilst we acknowledge there will be initial upfront costs to be met, if implemented, the guideline will improve patient outcomes and is cost-effective to the NHS in the long-term; NICE's cost impact assessment projects a saving of approximately £14 million per year in England, before implementation costs. This has now been emphasised in the guideline introduction. The GC acknowledge that the expected cost savings in unnecessary drug treatment for asthma (through more accurate diagnoses) will be realised at the CCG-level, and not by individual GP practices. It is outside of the GC's remit to recommend how services should be organised; however, the GC expect that CCGs would support GP practices to implement the guideline e.g. purchase of FeNO machines, to achieve cost savings through economies of scale. This view is reflected in recommendation 1.3.1 on diagnostic hubs.
The Association of Respiratory Nurse Specialists	Full	44	28	Are NICE going to recommend that anyone with a restrictive pattern on spirometry is referred?	Thank you for your comment. No, the algorithms address the diagnosis of asthma, diagnosis of other conditions being beyond the scope of the guideline.
The Association of Respiratory	Full	45	10 & 17 & 24	On how many occasions in the 2-4 weeks do you want to see 20% variability?	Thank you for your comment. The percentage variability is calculated across the whole monitoring period. In the bigger studies of peak flow variability this was done for 1-2 weeks.

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Nurse Specialists					
The Association of Respiratory Nurse Specialists	Full	98	23	Is there to be any acknowledgement that people with ACO could display this level of reversibility and this needs to be considered as a differential diagnosis based also on the history?	Thank you for your comment. The concept of ACO is not universally accepted. There is not a clear definition for this putative condition and it remains outside the scope of this guideline.
The Association of Respiratory Nurse Specialists	Full	113	General	For all age groups in your recommendation box, as above, is a one off measurement of reversibility within the 2-4 weeks of monitoring sufficient and if so this needs to be made clear as currently no amount of times reversibility is seen is stipulated.	Thank you for your comment. For diagnostic purposes this is a one-off measurement, as with all the other recommended tests. There may be patients in whom it is thought appropriate to monitor PEF after this, but that is a different issue.
The Association of Respiratory Nurse Specialists	Full	144	Table 49	As per comment 7, the GC have expressed an opinion that the single cost of FENo per patient will be £10.01-£13.66. How are NICE going to ensure finances are in place to absorb these extra costs in healthcare settings?	Thank you for your comment. The GC's remit was to produce a clinical and cost-effective guideline on the diagnosis and monitoring of asthma, which the GC has fulfilled. Whilst we acknowledge there will be initial upfront costs to be met, if implemented, the guideline will improve patient outcomes and is cost-effective to the NHS in the long-term; NICE's cost impact assessment projects a saving of approximately £14 million per year in England, before implementation costs. This has now been emphasised in the guideline introduction. The GC acknowledge that the expected cost savings in unnecessary drug treatment for asthma (through more accurate diagnoses) will be realised at the CCG-level, and not by individual GP practices. It is outside of the GC's remit to recommend how services should be organised; however, the GC expect that CCGs would support GP practices to implement the guideline e.g. purchase of FeNO machines, to achieve cost savings through economies of scale. This view is reflected in recommendation 1.3.1 on diagnostic hubs. The wording of this recommendation has been changed to make it clearer who the recommendation is aimed at. GPs use Diagnostic hubs or hospital services for other conditions (e.g. x-rays and echocardiograms) so it is not unreasonable to suggest that the same might be done for asthma tests.
The Association of Respiratory Nurse Specialists	Full	206	4.0 and 4.1 in recommendations box	How will clinicians know if the person's asthma is "suboptimal" if they have not already used an assessment tool such as the ACT/ACQ etc, as NICE have already identified that health professionals and patients do not recognise "control" with normal questioning? It should therefore be recommended not just "considered" to use a tool on all adults ideally one that is validated and age appropriate ones on children.	Thank you for your comment. The word 'consider' is used to reflect the strength of the evidence behind the recommendation for the Asthma Control Questionnaire or Asthma Control Test.
The Association of Respiratory Nurse Specialists	Full	44 & 190	11 & 26	There are concerns that by promoting diagnostic hubs that many areas will become deskilled in the diagnostic process which could have a detrimental effect on patients.	Thank you for your comment The recommendation on diagnostic hubs is a suggestion only about how the guideline could be implemented. Those practices currently able to provide this diagnostic service can continue doing so, and those who are currently not able to can either make the investment to offer this service or utilise diagnostic hubs. If they choose the latter they will receive the test results, in the same way as they might receive a chest x-ray report.
Thermo Fisher Scientific	Full	40	General	Initial clinical assessment algorithm *Thermo Fisher Scientific Response* If allergen specific IgE testing is considered as part of the diagnostic work up further down the management process, then further explanatory information needs providing to enable GPs and other physician's clear guidance on the use of these tests. The 'NICE Asthma Management' guideline that is in tandem development	Thank you for your comment. We do not agree that there is a conflict between this guideline and the NICE Asthma Management guideline. This guideline states that allergen testing can be used once asthma is diagnosed, to help identify environmental asthma triggers. In the opening recommendation of the asthma

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				should be linked to the initial assessment algorithm (and this guideline). Allergic asthma is the most common form of asthma (as stated on page 117 of this guidelines) so confirmation of atopy and allergen identification/ exposure reduction should include as part of an asthma management plan. - Thermo Fisher Scientific commented previously on the 'NICE Asthma Management Guidelines' with supporting medical evidence for allergen identification and exposure reduction. The NICE management guidelines (consultation February 2017) currently does not consider specific IgE tests and exposure reduction as part of overall asthma management. We perceive this as a conflict between the two set of NICE asthma guidance, and therefore the 'Diagnosis and Monitoring Guidelines' should further elaborate and clarify allergy testing as part of overall asthma management.	management guideline, factors which might contribute to poor asthma control are listed, including environmental factors. You ask for clear guidance on use of allergen tests, but in practice they must be individualised for each patient depending on their exposures.
Thermo Fisher Scientific	Full	43	22	Use of specific IgE tests in asthma assessment *Thermo Fisher Scientific response* Thermo Fisher Scientific welcomes the statement that 'specific IgE (or RASTs) are not asthma diagnostics'. These tests are allergen sensitisation tests and add clinical value by aiding clinical assessment to confirm atopic allergy and the underlying allergen triggers that can cause asthma.	Thank you for your comment.
Thermo Fisher Scientific	Full	43	28	Specific IgE and Skin Prick Tests *Thermo Fishers Scientific response* The GC refers to the use of in-vitro and skin prick tests (SPT) within the overall document and recommends that if indicated, *'use skin prick tests to aeroallergens or specific IgE tests to identify triggers after formal diagnosis of asthma has been made'*. If allergen specific IgE testing is recommended within the guideline it is our opinion that GPs and other medical professionals need further clarity on the use of these tests. This includes, what common aero allergens to test for, interpretation and supporting information on allergen exposure reduction as part of asthma management. See further responses below	Thank you for your comment. This is outside the scope of this guideline.
Thermo Fisher Scientific	Full	133	General	Allergen identification and exposure reduction *Thermo Fisher Scientific response* As stated in previous comments above we welcome the statement that '*it was noted that there are circumstances in which it is extremely useful to know which allergens a person with asthma is sensitised to. This can be useful therapeutically, for example in terms of avoiding exposure and therefore triggering an attack'*. - Again the consideration for allergen identification and management should be considered in the 'NICE Asthma Management guidelines' and linked to this guideline for clarity and a holistic approach to asthma diagnosis and management.	Thank you for your comment. This Diagnosis & Monitoring guideline states that allergen testing can be used once asthma is diagnosed, to help identify environmental asthma triggers. In the opening recommendation of the Management Guideline factors which might contribute to poor asthma control are listed, including environmental factors. The link is therefore already present.
University Hospitals of	Clinical			Pragmatic. This is a non-pragmatic, ivory tower led guidance that fails to understand that asthma diagnosis is, always has been and	Thank you for your comment. We agree that asthma diagnosis should be based on history backed up by objective tests. Your phrase "where possible" is telling. The feasibility study has shown that it is possible to use

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Leicester NHS Trust	diagnosis			always will be a clinical diagnosis backed up by objective tests and observations where possible. It unfortunately relies too much on objective tests for primary care to use if appropriately and is moving asthma diagnosis towards secondary care…..the NHS is not in a position t deliver this. A better approach would have been to work closely with the BTS to tackle to barriers to effective guideline implementation in the UK and improved diagnosis using the existing guidance. NICE and the committee have shown themselves to be arrogant, detached, unhelpful and blinkered in their approach. This guidance is likely to lead to a reduction in asthma diagnosis but not an improvement and so have a negative impact on patients and more importantly patient safety.	objective tests far more than is done in current practice. Greater use is highly likely to improve diagnostic accuracy with a reduction in false asthma diagnosis, not a reduction in correct diagnosis. This will therefore have a positive impact on patients since those with a false diagnosis are on treatment they do not need and may well have some other, unaddressed, cause of their symptoms.
University Hospitals of Leicester NHS Trust	Exercise asthma			The assumption that exercise induced broncho-constriction only comes on after exercise is clinically and scientifically incorrect. The entire section around exercise related symptoms is poorly written, poorly researched and clinically unhelpful. Whilst it is true that not all exercise symptoms are asthma a more detailed section around exercise, alternate diagnoses and tests that can be used would have been more helpful. This section remains unfit for purpose	Thank you for your comment. The GC acknowledge that asthma can cause breathlessness during exercise, as well as after, and we have amended the clinical introduction to the chapter on symptoms after exercise to reflect this. However, whilst there are numerous causes for breathlessness during exercise, worsening after exercise is not common in other conditions, hence the GC wished to look at the diagnostic value of this symptom.
University Hospitals of Leicester NHS Trust	Full			Use of exhaled nitric oxide in the diagnostic algorithm. Whilst this is a huge improvement on the previous, quite ludicrous guidance, it remains a fact that primary care throughout the UK has neither access to nor funding to provide measurement of exhaled nitric oxide. Indeed in many areas access to good quality spirometry remains an issue. Whilst the guidance does prioritise spirometry it should not have left FeNO with such a prominent position and this will lead to confusion. The cost of providing FeNO for all suspected asthma diagnoses cannot be funded under current NHS Financial constraints and so guidance around this should not be delivered unless NHS England has agreed that this should be funded. Primary care is at financial breaking point and if practices are expected to fund this then many will either make cuts elsewhere or simply close. It is likely that the cost of providing this as a service will outstrip any perceived savings on prescription costs and perversely a guidance intended to improve cost effectiveness in asthma care is likely to significantly increase the cost of asthma diagnosis and management. This is not good for anyone.	Thank you for your comment. The GC's remit was to produce a clinical and cost-effective guideline on the diagnosis and monitoring of asthma, which the GC has fulfilled. Whilst we acknowledge there will be initial upfront costs to be met, if implemented, the guideline will improve patient outcomes and is cost-effective to the NHS in the long-term; NICE's cost impact assessment projects a saving of approximately £14 million per year in England, before implementation costs. This has now been emphasised in the guideline introduction. The GC acknowledge that the expected cost savings in unnecessary drug treatment for asthma (through more accurate diagnoses) will be realised at the CCG-level, and not by individual GP practices. It is outside of the GC's remit to recommend how services should be organised; however, the GC would expect that CCGs would support GP practices to implement the guideline e.g. purchase of FeNO machines, to achieve cost savings through economies of scale. This view is reflected in recommendation 1.3.1 on diagnostic hubs. The wording of this recommendation has been changed to make it clearer who the recommendation is aimed at (CCG's). GPs use diagnostic hubs or hospital services for other conditions, so it is not unreasonable to suggest that the same might be done for asthma tests.
University Hospitals of Leicester NHS Trust	Full			Demeaning the usefulness of blood eosinophilia. The full blood count as a test for diagnosis of either asthma or breathlessness on exertion has been woefully under-represented in this guidance. The presence (in untreated / steroid naïve individuals) of a raised peripheral blood eosinophil count remains an important diagnostic marker for asthma and the guidance provided here is factually, scientifically and clinically unhelpful. The presence of co-morbid disease such as anaemia or infection is also helpful and the low cost, easy access to an FBC makes it a very useful test where doubt persists. This statement is clinically unsound in the guidance.	Thank you for your comment. The GC reviewed the literature on measurement of blood eosinophils, and, for the reasons set out in the full guideline did not consider this added enough to the other tests that are included in the diagnostic algorithm. To summarise: the papers do not show a clear diagnostic cut-offpoint; the optimum cut-off point showed low sensitivity; a blood test is involved which is best avoided in children; and FeNO gives a measure of airway inflammation whereas blood eosinophils are not airway specific.
University Hospitals of Leicester NHS Trust	Full			Confusion. The guidance as it currently stands will be unable to be used by the vast majority of primary and a lot of secondary care in England and across the UK. With funding for the tests necessary to	Thank you for your comment. Please see our response above to your very similar comment in ID41.

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				follow the guidance unlikely to be forthcoming it is likely the guidance will be ignored for the most part.	

**None of the stakeholders who comments on this clinical guideline have declared any links to the tobacco industry.*