



Comparative Effectiveness Review Disposition of Comments Report

Research Review Title:

The Clinical Utility of Fractional Exhaled Nitric Oxide (FeNO) in Asthma Management

Draft review available for public comment from April 20, 2017 to May 15, 2017.

Research Review Citation: Wang Z, Pianosi P, Keogh K, Zaiem F, Alsawas M, Alahdab F, Almasri JM, Mohammed K, Larrea-Mantilla L, Farah W, Daraz L, Barrionuevo P, Gunjal S, Prokop LJ, Murad MH. The Clinical Utility of Fractional Exhaled Nitric Oxide (FeNO) in Asthma Management. Comparative Effectiveness Review No. 197 (Prepared by the Mayo Clinic Evidence-based Practice Center under Contract No. 290-2015-00013-I). AHRQ Publication No. 17(18)-EHC030-EF. Rockville, MD: Agency for Healthcare Research and Quality. December 2017. www.effectivehealthcare.ahrq.gov/reports/final.cfm. DOI: <https://doi.org/10.23970/AHRQEPCCER197>.

Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each research review is posted to the EHC Program Web site or AHRQ Web site in draft form for public comment for a 3-4-week period. Comments can be submitted via the Web site, mail or E-mail. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.



Commentator & Affiliation	Section	Comment	Response
TEP #1	Introduction	In the introduction and elsewhere there seems to be a lack of mention of the relationship of elevated FeNO to both atopic-allergic rhinitis and to rhinosinusitis. Both of these factors can enormously confound the studies in relation to asthma diagnosis and should be discussed in greater detail.	We thank the reviewer for the comments. We added this to the introduction.
TEP #1	Introduction	There are a few references in the text regarding FeNO as a surrogate for eosinophilic inflammation. Although there are some data to support parallel changes, there are no data to suggest one is dependent mechanistically on the other. Perhaps a small section on this complex relationship would be beneficial for the audience. Anti-IL5 will nearly eliminate eosinophils and has no effect on FeNO. While a full review of the relationship between anti-IL5 and FeNO may be beyond the scope of this version, using it as background data would seem to be needed at least, especially since the data have been around for nearly 10 years and the anti-Il-5s are now on the market.	We thank the reviewer for the comments. We added a section about the association between FeNO and eosinophilia/Th2 inflammation to the introduction.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Introduction	This is generally well stated though the main point, that asthma diagnosis is difficult, is in paragraph two. In fact, the first sentence is used in the vast majority of asthma manuscripts and is boring. It might be reasonable to start off with the diagnosis dilemma. The first word of paragraph 2 is misspelled	We thank the reviewer for the comments. This report is one of 4 reports for NHLBI's upcoming asthma guideline. We are coordinating to have a consistent structure in the introductions across 4 reports. We corrected the misspelled word. We have added diagnostic dilemma to the introduction section.
TEP #2	Introduction	Well written with no issues.	We thank the reviewer for the comments.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Introduction	<p>Well-written and puts the problem and the key questions in perspective in the field of asthma.</p> <p>On page 1, line 39, suggest remove "with asthma" so that the sentence reads "In young children, the diagnosis of asthma is particularly..."</p> <p>On pages 2-3, suggest moving KQ1e to KQ1b, so that the first 2 bullet points deal with diagnosing asthma. Then the rest of the bullet points KQ1c-e deal with the utility of FeNO in the management and monitoring of asthma.</p>	<p>We deleted "with asthma".</p> <p>For numbering KQs, we prefer to keep the same order we had in the protocol. The order is logical and follows a-diagnostic accuracy then b-clinical utility then c-predicting for asthma.</p>
Peer Reviewer #3	Introduction	Well done.	We thank the reviewer for the comment.
Peer Reviewer #4	Introduction	The introduction is concise and generally well written.	We thank the reviewer for the comment.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	Introduction	<p>Historically, there is a lot of important material between refs 6 and 7. Two may be worth citing. The first is a paper that was presented in Germany the same day as ref 6, but published the next year: Gaston B, Massaro A, Drazen J, Chee CBE, Wohl MEB, Stamler JS. Expired nitric oxide levels are elevated in patients with asthma. In S. Moncada, M. Feelisch, R. Busse and E.A. Hibbs, eds, <i>Biology of Nitric Oxide</i> (vol 3), London: Portland Press (1994), 497-499.</p> <p>Second, the first paper showing FENO to be abnormal in children was, Nelson BV, Sears S, Woods J, Ling CY, Hunt J, Clapper LM, Gaston B. Expired nitric oxide as a marker for childhood asthma. <i>J Pediatr</i> 1997;130:423-427.</p> <p>Mechanistically, it is worth noting that iNOS activity is not always the direct determinant of ENO. Activated airway eosinophils, for example, are associated with increased FENO but do not necessarily have increased iNOS activity. Important modulators include airway pH, airway redox status, airway S-nitrosothiol metabolism, airway microbial colonization and airway heme. There are many papers on these determinants; most are reviewed in Marozkina NV, Gaston B. Nitrogen chemistry and lung physiology. <i>Ann Rev Physiol</i> 2015; 77:431-52</p>	We thank the reviewer for the comments. We added the first two references. For the third point, we focused on empirical clinical data following the key questions rather than on physiology and biology details.



Commentator & Affiliation	Section	Comment	Response
TEP #3	Introduction:	Page 11 Line 24-25 mentions “priority topic” and line 29-30 mentions “priority area” Consider changing to "topic" or "area" in both lines.	This report is one of the four reports to support NHLBI’s upcoming asthma guideline. All of the 4 reports used the paragraph for these sentences.
TEP #1	Methods	I have no concerns with the methodology.	We thank the reviewer for the comments.
Peer Reviewer #1	Methods	This is excellent. It is explained clearly and the rationale for including or excluding manuscripts and data is well detailed.	We thank the reviewer for the comments.
TEP #2	Methods	Methods were explicit and well described; i can not comment on the statistical testing and assume an independent statistician will review.	We thank the reviewer for the comments.

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Peer Reviewer #2	Methods	<p>The methods are explicit and clearly stated. The inclusion and exclusion criteria are justifiable.</p> <p>The definition of asthma exacerbation should be given. In some sections the authors talk about asthma exacerbations only. In other, they talk about asthma exacerbations and asthma exacerbations requiring oral steroids (for example in page 21). I think defining asthma exacerbations at the start of each section where they use this as the outcome should be performed.</p>	<p>Asthma exacerbations were defined differently across studies. We used the definition provided in each study. The exception is in the KQ 1c where we actually had enough quantitative data (14 RCTs) and we were able to do meta-analysis and provided a classic SOE table. In this case, we have specifically defined “steroid requiring exacerbation” and “any exacerbation”. This is explicitly described in the SOE table (Table 5 in the full report).</p>
Peer Reviewer # 3	Methods	Statistical methods appear adequate.	We thank the reviewer for the comments.
Peer Reviewer #4	Methods	Methods are appropriate. The incl/excl criteria are acceptable. The search strategy was appropriate and would be expected to supply a comprehensive data set.	We thank the reviewer for the comments.

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Peer Reviewer #5	Methods	Exceptional. No suggestions.	We thank the reviewer for the comments.
TEP #3	Methods:	I do not see any deficiencies in the Methods section. Some typos are as below. Page 15 Line 8 - delete first word will Line 46 — Put space between "and device" Line 54—Correct spelling of "Coimparative"	Thank you. Typos are corrected



Commentator & Affiliation	Section	Comment	Response
TEP #1	Results	KQ1a. It would be helpful if the starting demographics of the population in which FeNO was studied would be listed with the study. A summary of these and their relation to sensitivity/specificity of FeNO testing could be developed into a table and put in the main text.	We added a table to summarize the number of studies by age group (Table 2 in full report). The demographics of the population of the included studies is listed in Appendix C. The summary of the demographics is listed at the beginning of the section. We were able to conduct subgroup analysis based on age (<18 vs. >=18) (Appendix E 4). We were unable to evaluate other demographics due to lack of reporting.



Commentator & Affiliation	Section	Comment	Response
TEP #1	Results	Section 1c-d are very well written, the tables are helpful and easy to understand and the utility (or lack thereof) of the test in the various situations clearly spelled out. Section 1a is the most confusing (as alluded to above) and it would be helpful to add an additional table.	Section 1a follows a standard quantitative diagnostic meta-analysis. It starts by describing the studies, followed by text and figures that show the risk of bias, then a table with the diagnostic meta-analysis estimates for sensitivity, specificity, likelihood ratios and a description of the SOE (ie certainty in estimates).
TEP #1	Results	The Tables in the Appendix are full of a wealth of summarized information. However, it would be beneficial to divide the tables further into subquestions for easier search.	The tables in the appendix follow a standard EPC format (search strategy, excluded studies, description of included studies (organized by KQ), risk of bias (organized by KQ), and of course there are tables of subgroup and sensitivity analyses).

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Peer Reviewer #1	Results	<p>There are some very interesting findings in this paper and it would be nice to highlight the key ones more strongly, if possible. The following results will have significant impact in the field:</p> <ol style="list-style-type: none">1. FeNO has a remarkably good specificity for diagnosis of asthma at FENO levels in 50 ppb range2. FeNO can be a marker of drug response to ICS and LTRA.	<p>Thank you for the nice comments. We agree with your inferences and the current key points actually reflect these concepts.</p>
TEP #2	Results	<p>It is well done. I was able to follow the authors rational for study inclusion and the tables helped clarify who/what was included and excluded.</p>	<p>We thank the reviewer for the comment.</p>
Peer Reviewer #2	Results:	<p>I think the results are clearly presented.</p> <p>On page 8, lines 22-23: the statement should be clarified. I suggest changing so that it reads as follows:</p> <p>9 studies addressed KQ 1.e about the predictive ability of FeNO measures in children < 5 years on the development of asthma in children > 5 years.</p> <p>As suggested above, I recommend that KQ1e be moved to KQ1b.</p>	<p>Thank you. We changed the sentence accordingly. We prefer to keep the same order we had in the protocol. The order is logical and follows a-diagnostic accuracy then b-clinical utility then c-predicting for asthma.</p>



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results	<p>Is the amount of detail presented in the results section appropriate? YES Are the characteristics of the studies clearly described? YES Are the key messages explicit and applicable? MOSTLY SO. PLEASE SEE MY COMMENTS IN CLARITY AND USABILITY.</p> <p>Are figures, tables and appendices adequate and descriptive? YES Did the investigators overlook any studies that ought to have been included or conversely did they include studies that ought to have been excluded? NO</p>	We thank the reviewer for the comment.
Peer Reviewer #4	Results	This report has a compact results section which is a plus. The displays are easy to interpret for a reader who has general skills in this area. No evidence that important studies were missing. Figure, tables and appendices are fine.	We thank the reviewer.
Peer Reviewer #5	Results	Well-reasoned.	We thank the reviewer.



Commentator & Affiliation	Section	Comment	Response
TEP #3	Results:	<p>One thing is unclear to me and perhaps to other readers. The authors report average age which is written as a range rather than how average is usually reports as a mean and standard deviation.</p> <p>Some typos are as below.</p> <p>Page 18 Line 51— Correct error "<20pbb"</p> <p>Page 20 Line 38 — Spell check "Visual"</p> <p>Page 23 Line19 — Spell check "Association"</p> <p>Page 25 Line 32 — Space in "they lost" Line 47 — spell check "visitis"</p> <p>Page 33 Line 47— Spell out the "QALY" abbreviations</p>	<p>The problem stems from the use of aggregated data. Technically, we only know the average age reported by the included studies and reported the range of average age. We believe this is a more accurate. We corrected the typos.</p>



Commentator & Affiliation	Section	Comment	Response
TEP #1	Discussion/ Conclusion	<p>The discussion focuses on the main issues. However, again concerns arise from the seemingly incomplete understanding of the relationship between atopy, eosinophilia, Type 2 inflammation and FeNO. In addition to eosinophilia, a relation to Type-2 inflammation (IL-4/13, but NOT IL-5) should be added. It would help the reader greatly to better understand these complex relationships.</p>	<p>We added in a paragraph to the introduction addressing the relationship between FeNO and atopy, type 2 inflammation, IL4 ,IL5 , and IL13. The available data supports what the reviewer says to some extent; but is limited, and there are further clinical trials not yet published looking at anti-IL5 and FeNO. Anecdotally in our clinical practice, FeNO has dropped with anti-IL5 therapy. Studies on other monoclonals targeting IL5 (on the market) and IL4, 13 trials, did not meet criteria for inclusion in this review and discussing them further is beyond the scope of this review.</p>

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Peer Reviewer #1	Discussion/ Conclusion	The discussion needs focus and emphasis on the key results. It is written almost as a summary, and in the order, of the results. It would be more meaningful and have more impact if it focused on the clinical utility of FeNO. In this sense, it would be important to see emphasis on the more clear positives of FeNO first, and then comment on where FeNO seems to be less useful. More interpretation of the results is needed.	The discussion follows the order of Key Questions. We added several paragraphs to address clinical utility of FeNO to help in the interpretation. We presented 2 common scenarios in which FeNO is most helpful.
TEP #2	Discussion/ Conclusion	Well written section with reasonable suggestion for needed research	We thank the reviewer for these comments.
Peer Reviewer #2	Discussion/ Conclusion:	Discussion and conclusion section is well-written and reflects the findings in the body of the paper.	We thank the reviewer for these comments.
Peer Reviewer #3	Discussion/ Conclusion	<p>The discussion is well done and is clearer than the abstract and summary.</p> <p>Please consider the following. Are the implications of the major findings clearly stated? YES Are the limitations of the review/studies described adequately? YES</p> <p>In the discussion, did the investigators omit any important literature? NO</p> <p>Is the future research section clear and easily translated into new research? VERY WELL DONE.</p>	We thank the reviewer for these comments.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Discussion/ Conclusion	Findings were clearly stated and interpreted appropriately. Future research question is clear. No concerns.	We thank the reviewer for these comments.
Peer Reviewer #5	Discussion/ Conclusion	In terms of future directions, it is exceptionally important to get at the biological determinants of FENO. Clinical utility of the test will always be marginal unless we know specifically why it is abnormal in a specific patient.	We added sentences about factors that may affect FeNO testing in the future research needs.
TEP #3	Discussion/ Conclusion:	Some minor typos Page 42 Line 31 — Space "inasmuch" Page 43 Line 25— Change "this" to "these heterogeneous findings"	Typos are corrected.
TEP #1	Clarity and Usability	The structure is appropriate	We thank the reviewer for these comments.
Peer Reviewer #1	Clarity and Usability	Yes, this is an easily readable manuscript and the impact is clear. The results and methods sections are well organized. The discussion was disappointingly bland however and recommendations are included above.	We thank the reviewer for these comments.

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TEP #2	Clarity and Usability	It is well organized but rather dense. The authors attempt to format the Key questions to ease interpretation but they are still difficult to distill. The discussion/conclusion did not include the cost effectiveness information which is very important to payors and thus to clinicians and patients. I am concerned this will be too dense for clinicians to find useful. Can there be additional tables or perhaps clinical scenerios from that data to illustrate when or how FENO could be useful? For example using FENO to diagnose asthma via the various cut offs with sens/spec displayed? Would the authors advocate a range of cut offs i.e. <20 to rule out asthma and >40 to rule it in with 20-40 indeterminate	We have presented the few available studies on cost effectiveness. We have presented sensitivities/specificities per FeNO cutoff (table 2). In the revised report, we added some clinical scenarios in which FeNO would be most helpful as reviewer suggested. We do not make clinical recommendations in a SR. NHLBI will use the report to develop clinical practice guidelines.

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TEP #2	Clarity and Usability	<p>? Are there clinical situations where using FENO is supported by data and potentially by cost: using FENO in addition to asthma control measures to adjust medications in allergic asthmatics with frequent exacerbations? Others? I guess the question is based on all this data in what situations would the authors suggest FENO measurements are of value and cost effective? All asthma visits? Some and if so which ones? Many clinicians remain unsure of how/when to use FENO and many commercial payors won't reimburse as it is "experimental". The data here suggests there are patients and clinical situations where there is data to support its use and that is the message I would try to clarify in a more readable fashion for the average non statistical savvy clinician (if possible).</p>	<p>As the reviewer notes, data is only one factor in making recommendations for when FeNO should be used. This systematic review is on the evidence for the accuracy of FeNO. NHLBI will use the information from this review to make recommendations for when to use FeNO based on other considerations suggested by the reviewer. Asthma can sometimes be a difficult diagnosis to make and FeNO can be helpful – more so in ruling in, than ruling out based on the sensitivity and specificity of the test.</p>



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TEP #2 (continued)			<p>In a patient whose FeNO is initially elevated, data supports that it can be helpful to follow it in regards to response to therapy, particularly inhaled steroids and LTRA. This is typically applicable to patients with atopic/eosinophilic asthma.</p> <p>We added discussion on the interpretation of the findings from a clinical context.</p>
Peer Reviewer #2	Clarity and Usability:	The report is generally well structured and organized, except for the issues I brought up above. This will be a very useful report for those who manage asthma patients and those who perform research on asthma.	We thank reviewer for these comments.

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Peer Reviewer # 3	Clarity and Usability	<p>The authors have done an admirable job bringing together a diverse literature. The clinical meaningfulness of the report is limited by the heterogeneity of the populations studied and the reference interventions. The authors have done a good job of discussing the difficulties and the nuances in their discussion but that could come through more clearly in the abstract and the summary sections. For diagnosis there seem to be several different questions that are clinically meaningful: What is the diagnostic utility of the test in picking up asthma in a general population not on any type of treatment? What is the diagnostic utility in a population with symptoms not on ICS? It would be useful to discuss these issues separately and discuss the interpretability of the answer for each of these questions relative to the diagnostic tests used to make the diagnosis. In reference to use in management, this section would benefit from further discussion of the comparison methods used to manage the patients.</p> <p>I have listed some specific issues below some of which relate to the general issue discussed above. I have referred to the PDF pages P6, L 27-28 – Words missing</p>	<p>The study protocol and questions was developed at the beginning of the study and was used to guide the whole research progress. We agree that the questions are important. We added sentences in Suggestions for Future Research. ICS naïve was evaluated in the sensitivity analyses. We corrected the typos and clarified sentences.</p> <p>Abstract: FeNO test and reference tests were used to diagnose suspected asthma patients. We revised the sentence. Abstract: compared to no FeNO and it is corrected</p>



Commentator & Affiliation	Section	Comment	Response
<p>Peer Reviewer #3 (continued)</p>		<p>L 25-26 – Sentence unclear. Does <20 increase the likelihood?</p> <p>32-33 – If the diagnosis is asthma, how can diagnostic accuracy be better in steroid naïve asthmatics vs. the general population if the former group is already defined as having the disease?</p> <p>41-42 Reduced risk of exacerbations compared to what?</p> <p>P18</p> <p>L 50-54 - I am confused as to how including value <20 for diagnostic accuracy makes sense. I assume that what we mean is a cut-off >20 as positive rather than <20 for positive.</p> <p>P19</p> <p>L7-9 – I assume we are saying that the cutoff is what yields the highest diagnostic accuracy, not that the cutoff of 20 is most accurate in steroid-naïve as compared to non-steroid naïve. Please clarify.</p> <p>P22</p> <p>L36-38 – It would be worth elaborating on the quantitative differences between comparison to healthy vs. symptomatic since this is critical diagnostically.</p> <p>General re Use in Management Algorithms</p> <p>It would be helpful to distinguish what management algorithms were used in comparison to nitric oxide.</p>	<p>Results:</p> <p>KQ 1a Key points: We mean the cutoffs reported by the studies below <20 ppb. These included different cutoffs, not one value. In the example, a cutoff 20 ppb, any testing value above is positive, and below is negative.</p> <p>The cutoffs <20 ppb, FeNO had the highest accuracy in steroid naïve patients compared to patients in the main results. We modified the sentences.</p> <p>KQ1a Subgroup and sensitivity analyses: We added quantitative differences between comparison to healthy vs. symptomatic Management algorithms are described in details in appendix table I.2</p>

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Peer Reviewer #4	Clarity and Usability	This report is generally clear and concise. There are several typos that should be addressed in review.	In this revision, we hope we have corrected those typos.
Peer Reviewer #5	Clarity and Usability	A bit dense, but comprehensive.	We thank reviewer for these comments.
TEP #3	Clarity and Usability:	Very clear report. The high strength of evidence of using FeNO in asthma management algorithms may allow its routine use in clinics.	We thank reviewer for these comments.
TEP #1	General	Overall this is a timely and well written summary of the utility of FeNO under a variety of situations/conditions. The questions addressed are relevant and clear. It should be a helpful guide for clinicians and researchers.	We thank reviewer for these comments.
Peer Reviewer #1	General	This is important work that will be widely cited. A review that analyzes the strength of the evidence in many of these areas has been needed. The questions that parse how FeNO can be used diagnostically, for asthma management, and to assess response to drugs are the critical ones. Some questions are less important clinically, e.g. use in kids under age 4, but it is reasonable to include given that there is literature to interpret.	We thank reviewer for these comments.

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TEP #2	General	This is an excellent and useful report. The key questions are answered and the authors did an excellent job of explaining their decision making process. Some grammar/syntax in abstract and results sections need reviewed.	In this revision, we hope we have corrected those typos/grammar problems.
Peer Reviewer #2	General	<p>Additional Questions: Quality of the Report: Superior</p> <p>The report is well-written and the methods used were clearly stated. The Key Questions are also clearly defined, explicitly stated, and appropriate. Key Question 1a and KQ1e are related, in my mind, in that they both deal with the use of FeNO in the diagnosis of asthma. I think the authors can move KQ1e after KQ1a, then move the other questions down. I also would like the authors to clarify the cutoffs in the manuscript. These are detailed below.</p>	For numbering KQs, we believe this is not critical and prefer to keep the same order as originally proposed by NHLBI that starts with diagnosis, followed by utility and then prediction. Cutoffs were clarified in the report.
Peer Reviewer # 3	General	<p>The questions are very well stated. The audience is well defined. The clinical meaningfulness of the report is limited by the heterogeneity of the populations studied and the reference interventions.</p>	We thank reviewer for these comments.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	General	<p>Quality of the Report: Good</p> <p>This report assesses FENO use in diagnosis, monitoring activity, treatment selection; which is clinically important. The target population is well explained. The key questions are stated explicitly and are appropriate.</p> <p>I did not find the an explicit description of the intended audience</p> <p>No other concerns.</p>	The intended users are clinical practice guideline developers.

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TEP #3	General	<p>Quality of the Report: Superior</p> <p>The reports is very meaningful as it is studying a disease which affects large number of people of all age groups. This report is ever so important due to the morbidity posed by Asthma especially in the non adult population where it is a leading illness.</p> <p>The key questions were appropriate and explicitly stated and applied upon an explicitly defined population. However the KQ1b is a rather difficult question to study as asthma control can be measured in numerous ways. Authors should have studied this question in greater detail or should address this question more comprehensively in the "Suggestions for future research" section.</p>	<p>We agree that KQ1b is challenging and is based on narrative evidence synthesis. We added a sentence to the future research section about how studies evaluating disease activity and outcome, should use validated measures of activity and well defined outcomes.</p>



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	General	Murad and coworkers have produced a truly elegant and comprehensive analysis of the clinical utility and diagnostic accuracy of FENO measurement in asthma using data from 168 different studies. They find value in the test, particularly in predicting exacerbations, in steroid naïve subjects, children and nonsmokers. This work makes a substantial contribution that is relevant to clinical practice. This has been a huge amount of work and it is meticulously prepared. My only reservations have to do with the background/mechanism and with the future directions.	We made substantial changes in the background on mechanism and future research needs sections.
Public reviewer #1 [Marc Massanari, Pharm.D. Vice President, Global Medical affairs Circassia Pharmaceuticals, Inc.]		<p>The evidence to support monitoring FeNO in asthma management is considerable. Ever since 2000, FeNO monitoring has been increasingly included in many clinical trials evaluating potential new anti-inflammatory asthma drugs. Furthermore, a recent literature search of the National Library of Medicine's PubMed for asthma clinical studies involving FeNO, (using nitric oxide and asthma as search terms) produced over 3,000 articles.</p> <p>We applaud your comprehensive review of the evidence to support the use of FeNO monitoring in the management of asthma.</p>	Thank you.



Commentator & Affiliation	Section	Comment	Response
<p>Public reviewer #1 [Marc Massanari, Pharm.D. Vice President, Global Medical affairs Circassia Pharmaceuticals, Inc.]</p>		<p>The questions used in your review closely align with what we believe best support the rationale for monitoring FeNO in asthma management. However, there seems to be some overlap in your analysis between Key Questions 1. b, 1. c and 1. d that may cause readers confusion. Perhaps a better categorization based on literature evidence would be:</p> <ol style="list-style-type: none"> 1. Role of FeNO in the Diagnosis of Asthma by Identifying Patients with Th2 Airway Inflammation 2. Role of FeNO in Determining Steroid Responsiveness and Optimizing the Dose of Inhaled Corticosteroids 3. Role of FeNO as a Tool to Uncover Non-Adherence to Inhaled Corticosteroids 4. Role of FeNO Monitoring to Reduce the Likelihood of Exacerbations in Patients at Risk for Future Events 5. Role of FeNO to Identify Asthmatics Who Are Possible Candidates for Treatment with a Biologic. 	<p>The current KQs cannot be changed at this point because they follow a priori established protocol.</p>



Commentator & Affiliation	Section	Comment	Response
<p>Public reviewer #1 [Marc Massanari, Pharm.D. Vice President, Global Medical affairs Circassia Pharmaceuticals, Inc.]</p>		<p>KQ 1. a: What is the diagnostic accuracy of FeNO measurement(s) for making the diagnosis of asthma in individuals ages 5 and older?</p> <p>The analysis included a comprehensive review of studies using various reference comparators. However, none of the reference comparators (i.e., clinical diagnosis, spirometry, bronchial challenge, bronchodilator response, etc) directly measure Th2 driven airway inflammation. The only other biomarker of airway inflammation besides FeNO is sputum/blood eosinophils. It is not clear from Table 2 if any of the studies included a comparison to sputum or blood eosinophils. Incorporating biomarkers into the patient’s clinical evaluation uncovers untreated airway inflammation and assists practicing physicians to more accurately diagnosis asthma and properly classify the patient’s asthma phenotype. (Fajt 2015, Bush 2016). Though some consider evaluation of induced sputum for the presence of eosinophils a gold standard for detecting airway inflammation, this test is difficult to perform and not often performed in the majority of office based clinical practices. Its use is more common in specialized research centers equipped to perform the test.</p>	<p>Comparison with sputum or blood eosinophils was not the goal of the diagnostic question, and we were not interested in Th2 or other biomarkers. Our key question is focused on establishing a diagnosis of asthma. In terms of references studies: Sivan 2009, Smith 2004, Schleich 2012 were included in our analyses (KQ 1a, diagnostic). Hewitt 2008: does not include population of interest. Attanasi 2016: no outcome of interest (no diagnostic accuracy). Karrasch 2017 is a systematic review, not original study. Wagener 2015 Not relevant to key question.</p>

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<p>Public reviewer #1 [Marc Massanari, Pharm.D. Vice President, Global Medical affairs Circassia Pharmaceuticals, Inc.] (continued)</p>		<p>FeNO measurement has been directly evaluated in comparison with other diagnostic procedures for asthma including induced sputum for eosinophils, spirometry and bronchial challenge testing. FeNO has high sensitivity and specificity and correlates well with the results of induced sputum and bronchial challenge testing (Sivan 2009, Smith 2004, Hewitt 2008, Schleich 2012, Attanasi 2016). In a recent comparative meta-analysis of a variety of tests for diagnosing asthma (e.g. spirometry, bronchial challenge, and/or bronchial reversibility), FeNO was found to have good performance and the authors even stated that FeNO might render bronchoprovocation testing superfluous (Karrasch 2017). In addition, FeNO has also shown to be equivalent to the use of peripheral blood eosinophils as a surrogate to predict sputum eosinophils (Wagener 2015). While the combination of peripheral blood eosinophils and FeNO further improves the sensitivity and specificity of detecting airway inflammation to a modest degree (Westerhof 2015), FeNO alone provides sufficient accuracy of detecting Th2 airway inflammation and is available for use at the point of care (Wagener 2015).</p>	

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<p>Public reviewer #1 [Marc Massanari, Pharm.D. Vice President, Global Medical affairs Circassia Pharmaceuticals, Inc.]</p>		<p>KQ 1.b: What is the clinical utility of FeNO measurements in monitoring disease activity and asthma outcomes in individuals with asthma ages 5 and older?</p> <p>Adherence SOE was rated as low due to the observational nature of the studies. Typically adherence studies are not conducive to randomized controlled double blind studies, therefore real world evidence from observational studies should not be discounted as low evidence. Only three studies were cited as evidence in Table 3. The following studies provides additional evidence to support using FeNO to detect non adherence:</p> <p>See supplemental material for the reviewer's full letter which is text copied and pasted from: http://www.nichemedical.com.au/pdf/2017.05.FeNO%20Value%20Proposition%20White%20Paper%20-%20Circassia%202017.pdf</p>	<p>The reviewer's comment about randomized trials adherence being not conducive for evaluating adherence is incorrect (in fact, there are numerous randomized trials of adherence in various conditions). In the area of FeNO and adherence, the available studies are observational studies, hence SOE is low.</p> <p>The text provided by reviewer has references to other studies that indirectly can support an association between FeNO results and adherence (but less direct compared to the 3 studies we included in our report).</p>



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Public reviewer #1 [Marc Massanari, Pharm.D. Vice President, Global Medical affairs Circassia Pharmaceuticals, Inc.]		KQ 1.c: What is the clinical utility of FeNO measurements to select medication options (including steroids) for individuals ages 5 and older? See supplemental material for the reviewer's full letter which is text copied and pasted from: http://www.nichemedical.com.au/pdf/2017.05.FeNO%20Value%20Proposition%20White%20Paper%20-%20Circassia%202017.pdf	There are no specific comments in the pasted text. In general, the text discusses the burden of asthma exacerbations in terms of cost and also about plausible benefits of FeNO in predicting exacerbations. Studies relevant to KQ 1c are included in the report.



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<p>Public reviewer #1 [Marc Massanari, Pharm.D. Vice President, Global Medical affairs Circassia Pharmaceuticals, Inc.]</p>		<p>KQ 1.d: What is the clinical utility of FeNO measurements to monitor response to treatment in individuals ages 5 and older?</p> <p>See supplemental material for the reviewer's full letter which is text copied and pasted from: http://www.nichemedical.com.au/pdf/2017.05.FeNO%20Value%20Proposition%20White%20Paper%20-%20Circassia%202017.pdf</p>	<p>This comment consists of text copied from: http://www.nichemedical.com.au/pdf/2017.05.FeNO%20Value%20Proposition%20White%20Paper%20-%20Circassia%202017.pdf</p> <p>There are no specific comments in the pasted text. Specifically, the studies highlighted in this text: Andreson 2017: irrelevant to KQ, focuses on establishing a dose response for inhaled corticosteroid in asthma Nolte 2013: irrelevant to KQ, focuses on establishing a dose response for inhaled mometasone furoate/formoterol in subjects with asthma</p>

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<p>Public reviewer #1 [Marc Massanari, Pharm.D. Vice President, Global Medical affairs Circassia Pharmaceuticals, Inc.] (continued)</p>			<p>LaForce 2014: already included Hanania 2011: study evaluates the effectiveness of omalizumab and does not evaluate utility of FeNO Hanania 2016: abstract only. Hekking 2015, Kupczyk 2011 discuss difficult to treat asthma, irrelevant to KQs McNicholl 2012 study evaluates the effect of budesonide 1,600 µg on FeNO and correlates with FeNO reduction. It may provide indirect evidence regarding an association between FeNO and adherence. The 3 studies we included in the report about adherence are more direct. Massanari 2017: abstract about cost effectiveness</p>

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Public reviewer #1 [Marc Massanari, Pharm.D. Vice President, Global Medical affairs Circassia Pharmaceuticals, Inc.] (continued)			Pavord 2012: the aim of this trial is to evaluate the effectiveness of Mepolizumab and not the utility of FeNO. Overall, the white paper pasted in the comment is consistent with our findings about adherence.
Public reviewer #1 [Marc Massanari, Pharm.D. Vice President, Global Medical affairs Circassia Pharmaceuticals, Inc.]		KQ 1e: In children ages 0-4 years with recurrent wheezing, how accurate is FeNO testing in predicting the future development of asthma at age 5 and above? Technology to measure FeNO in children < 6yrs is currently not clinically available in the United States. Historically, the original NIOXR device allowed for collection of FeNO via tidal breathing. This device is no longer available. Current NIOXR devices, MINOR (which is being phased out) and VEROR are not able to collect FeNO via tidal breathing. However, Circassia has an active development program to address the ability to collect FeNO in younger children and toddlers.	No change is needed.

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<p>Public reviewer #2 [American Lung Association]</p>		<p>The American Lung Association appreciates the opportunity to submit comments with regard to the Agency for Healthcare Research and Quality (AHRQ) draft report for the systematic review on Fractional Exhaled Nitric Oxide (FeNO) Clinical Utility in Asthma Management conducted by AHRQ’s Evidence-Based Practice Center Program.</p> <p>The American Lung Association is the leading organization working to save lives by improving lung health and preventing lung disease through education, advocacy and research. The organization represents lung disease patients, their families, loved ones and caregivers. The Lung Association appreciates the analysis conducted with this report and believes it will contribute to our assessment of the proper use of this modality in care of the lung disease patients we advocate for. In review of the report, the Lung Association believes there is a need to have further emphasis on a specific area, namely: how obesity modifies FeNO. FeNO is usually low in obese patients and although this is mentioned in a line statement, nothing was discussed in the report as to how this can affect use of FeNO as a tool to predict exacerbations, use of medications, etc., in the obese patient population. With greater than two-thirds of the US adult population is now either overweight or obese, it seems that this area should be addressed. The report also includes very little strong evidence regarding FeNO for any measures other than decreased exacerbations. However, what do the data actually mean if we cannot track impact on hospitalizations, QOL, Asthma control and FEV1?</p>	<p>We appreciate the comments from the American Lung Association. BMI/weight was originally included in our study protocol. However, due to lack of reporting data on this variable (in studies that fit our inclusion criteria), we were unable to conduct such analysis. Future research should have better report on this. We also agree about the fact that strong evidence only exists for the outcome of exacerbation and that this is frustrating for decision makers. Our conclusions about this are similar to those made by the Cochrane Collaboration.</p>

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Public reviewer #2 [American Lung Association] (continued)		We also believe a clearer conclusion would be helpful to further the understanding of the importance of this document. Additionally, the implications for using FeNO in clinical care seem limited. It seems most likely that this test will have an impact in children rather than adults. The Lung Association respectfully thanks the AHRQ for conducting this report and for compiling all of the data from the various studies. We thank you for the opportunity to submit our comments and for your consideration.	In terms of conclusions and clinical implications, we added a paragraph describing 2 simple cases (clinical scenarios) in which FeNO would be helpful. There are of course other scenarios in which it would also be helpful). We thank The American Lung Association for the nice comments.