

Online supplementary Table S6b

QUESTION

Can measuring fractional exhaled nitric oxide (FeNO) help diagnose asthma in adults with episodic/chronic suggestive symptoms?	
POPULATION:	Population of adults (>18 yrs old) with diagnostic uncertainty of asthma
INDEX TEST:	FENO
GOLD STANDARD :	<ol style="list-style-type: none"> 1. Peak flow variability > 20% or spontaneous variation in FEV₁ > 12% and 200 ml between several clinic visits 2. Bronchodilation > 12% AND > 200 ml improvement 3. Airway hyperresponsiveness: PC20 < 16 mg/ml (or 8 mg/ml) of Methacholine (or Histamine) or PD mannitol < 625 mg or fall in FEV₁ > 10% after exercise 4. Improvement in FEV₁ > 12% and 200 ml after a 2-week course of OCS or a 4-week course of ICS

ASSESSMENT

Test accuracy How accurate is the test?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very inaccurate ○ Inaccurate ○ Accurate ○ Very accurate X Varies <ul style="list-style-type: none"> ○ Don't know 	<p>Based on Youden Index, recommended cut-off values for asthma diagnosis was ranging from 15 ppb to 46 ppb.</p> <p>For the cut-off value of 25 ppb (6 studies) the overall sensitivity value was 0.53 (95% CI: 0.33 to 0.72) and the overall specificity was 0.72 (95% CI: 0.61 to 0.81)</p> <p>For the cut-off value of 40 ppb (6 studies) overall sensitivity values was 0.61 (95% CI: 0.37 to 0.81) and the overall specificity value was 0.82 (95% CI: 0.75 to 0.87).</p> <p>For the cut off value of 50 ppb (3 studies) overall sensitivity was ranging from 0.19 to 0.56 and overall specificity was ranging from 0.77 to 0.95.</p>	<p>Given the wide range of recommended FeNO cut-off values for asthma diagnosis the panel decided to provide the overall sensitivity and specificity values for potentially the most useful cut-off values in clinical practice (25ppb, 40ppb and 50 ppb respectively).</p> <p>FeNO higher than 50 ppb is likely to indicate significant airway eosinophilia. It is also likely to indicate that a symptomatic patient has steroid-responsive airway inflammation. In this context, anti-asthmatic treatment could be started.</p>

		In a symptomatic adult patient with a FeNO of less than 25 ppb eosinophilic airway inflammation is unlikely. However, it does not discard asthma diagnosis.
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Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Trivial ○ Small ○ Moderate X Large ○ Varies ○ Don't know 	<p>-For the cut off value of 25 ppb, in the clinical context of primary care (pre-test probability 30%), out of 1000 patients tested, 159 corresponded to true positives and 504 corresponded to true negatives. In secondary care (pre-test probability 50%), out of 1000 patients tested, 265 corresponded to true positives and 360 corresponded to true negatives.</p> <p>-For the cut off value of 40 ppb, in the clinical context of primary care (pre-test probability 30%), out of 1000 patients tested, 183 corresponded to true positives and 574 corresponded to true negatives. In secondary care (pre-test probability 50%), out of 1000 patients tested, 305 corresponded to true positives and 410 corresponded to true negatives.</p> <p>-For the cut off value of 50 ppb, in the clinical context of primary care (pre-test probability 30%), out of 1000 patients tested, true positives ranged from 57 to 167 and true negatives ranged from 537 to 665. In secondary care (pre-test probability 50%), out of 1000 patients tested, true positives ranged from 95 to 278 and true negatives ranged from 537 to 665.</p>	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
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<ul style="list-style-type: none"> ○ Large ○ Moderate ○ Small <p>X Trivial</p> <ul style="list-style-type: none"> ○ Varies ○ Don't know 	<p>-For the cut off value of 25 ppb, in the clinical context of primary care (pre-test probability 30%), out of 1000 patients tested, 141 corresponded to false negatives and 196 corresponded to false positives. In secondary care (pre-test probability 50%), out of 1000 patients tested, 235 corresponded to false negatives and 140 corresponded to false positives.</p> <p>-For the cut off value of 40 ppb, in the clinical context of primary care (pre-test probability 30%), out of 1000 patients tested, 117 corresponded to false negatives and 126 corresponded to false positives. In secondary care (pre-test probability 50%), out of 1000 patients tested, 195 corresponded to false negatives and 90 corresponded to false positives.</p> <p>-For the cut off value of 50 ppb, in the clinical context of primary care (pre-test probability 30%), out of 1000 patients tested, false negatives ranged from 133 to 247 and false positives ranged from 35 to 163. In secondary care (pre-test probability 50%), out of 1000 patients tested, false negatives ranged from 222 to 405 and false positives ranged from 25 to 116.</p>	<p>Since asthmatic patients with no T2 airway inflammation do not present FeNO increase, it does not seem reasonable to use this tool to rule out asthma.</p>
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Certainty of the evidence of test accuracy

What is the overall certainty of the evidence of test accuracy?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very low ○ Low <p>X Moderate</p> <ul style="list-style-type: none"> ○ High ○ No included studies 	<p>-Sensitivity of the cut-off value of 25 ppb for the diagnosis of asthma was 0.53 (95% CI: 0.33 to 0.72) (Test accuracy (Grade): ⊕⊕⊕○ MODERATE). Specificity of the cut-off value of 25 ppb for the diagnosis of asthma was 0.72 (95% CI: 0.61 to 0.81); (Test accuracy (Grade) ⊕⊕⊕○ MODERATE).</p> <p>-Sensitivity of the cut-off value of 40 ppb for the diagnosis of asthma was 0.61 (95% CI: 0.37 to 0.81) (Test accuracy (Grade): ⊕⊕⊕○ MODERATE). Specificity of the cut-off value of 40 ppb for the diagnosis of asthma was 0.82 (95% CI: 0.65 to 0.87); (Test accuracy (Grade) ⊕⊕⊕○ MODERATE).</p>	<p>The systematic review revealed a best cut-off value (based on the Youden index) ranging from 15 to 46 ppb, presenting a wide range of sensibility and specificity values, showing a high variability between the results of the included studies.</p> <p>The heterogeneity of the presented results reflect a relevant limitation.</p>

	<p>-Sensitivity of the cut-off value of 50 ppb for the diagnosis of asthma was ranging from 0.19 to 0.56; (Test accuracy (Grade): ⊕⊕⊕○ MODERATE)). Specificity of the cut-off value of 50 ppb for the diagnosis of asthma was ranging from 0.77 to 0.95; Test accuracy (Grade): ⊕⊕⊕○ MODERATE).</p> <p>Not direct undesirable effects.</p>	
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Certainty of the evidence of management's effects

What is the overall certainty of the evidence of effects of the management that is guided by the test results?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very low ○ Low X Moderate ○ High ○ No included studies 	The included studies were retrospective cross-sectional and prospective cross-sectional studies.	If the result is positive, higher than 50 ppb, the probability of presenting asthma is higher.

Certainty of the evidence of test result/management

How certain is the link between test results and management decisions?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate X High ○ No included studies 	<p>If positive (above 50 ppb)- the management of asthma can be started and response to ICS can be expected to be good.</p> <p>If negative (below 25 ppb) patients could still benefit from asthma treatment (no T2 asthma) so it would not be wise to discard asthma or asthma treatment.</p>	The positivity of the test has been shown to be highly variable although above this limit (50 ppb) patients clearly benefit from starting asthma treatment.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
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<ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention X Favors the intervention ○ Varies ○ Don't know 	<p>If FeNO is performed and the test is positive, anti-asthma treatment can be started. There are not direct or indirect harms related to the test, so performing the test is clearly beneficial.</p>	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large costs ○ Moderate costs ○ Negligible costs and savings X Moderate savings ○ Large savings ○ Varies ○ Don't know 	<p>We did not look for evidence on costs.</p>	<p>Comparing to the rest of the tests used for asthma diagnosis, costs of performing FeNO do not exceed those required for the bronchodilator test or the bronchial provocation with methacholine.</p>
Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Reduced ○ Probably reduced X Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know 	<p>We did not look for evidence on equity.</p>	<p>There not seem to be equity issues related to this test.</p>
Acceptability Is the intervention acceptable to key stakeholders?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes X Yes ○ Varies ○ Don't know 	We did not look for evidence on acceptability.	No limitations identified related to acceptability, since it is an easy to perform, not time consuming, cheap and non-invasive technique. In this context the panel considers that the text is highly acceptable for patients, clinicians and policy makers.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes X Yes ○ Varies ○ Don't know 	We did not look for evidence on feasibility.	The panel considers that given the availability and the acceptable cost of performing FeNO, there are not limitations identified related to feasibility.

TYPE OF RECOMMENDATION

Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention •	Strong recommendation for the intervention ○
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CONCLUSIONS

Recommendation

The TF suggests measuring the fraction of exhaled nitric oxide (FeNO) as part of the diagnostic work-up of adults aged >18 years with suspected asthma (conditional recommendation for the intervention, moderate quality of evidence)

A cut-off value of 40 ppb offers the best compromise between sensitivity and specificity while a cut-off of 50 ppb has a high specificity >90% and is supportive of a diagnosis of asthma

A FeNO value <40 ppb does not rule out asthma and similarly high FeNO level do not define asthma

FeNO values are markedly reduced by smoking, treatment with ICS or anti-IL4/IL13-alpha antibody

Justification

Measuring FeNO is a point-of-care method that may be particularly useful in both primary and secondary care,⁵⁶ although it is not yet considered for reimbursement in most of European countries. A cut-off value above 40-50 ppb yields a high specificity (between 0.75 to 0.95), to rule in a diagnosis of asthma with confidence. However, the poor sensitivity (between 0.19 to 0.81) does not allow asthma to be ruled out, for values below 40 ppb. Although the TF recommends using FeNO to help in the diagnosis of asthma, we make it clear that high FeNO levels do not define asthma. High FeNO levels may be observed in patients with eosinophilic chronic bronchitis, allergic rhinitis or eczema who may deny any asthma symptoms and do not show bronchial hyperresponsiveness.

Subgroup considerations

FeNO is highly valuable in asthmatics with T2 inflammation although it is not useful for patients presenting no T2 inflammation. Its diagnostic accuracy is better for identifying eosinophilic asthma

Implementation considerations

The non-invasive and inexpensive nature of the technique make the implementation easy to perform in most clinical scenarios.

Monitoring and evaluation

Research priorities

Further studies analyzing the utility of FeNO in combination with other T2 biomarkers for asthma diagnosis.