

Online supplementary Table S11b

QUESTION

Can combining FeNO, blood eosinophils and IgE help diagnose asthma in adults with episodic/chronic suggestive symptoms?	
POPULATION:	Population of adults (>18 yrs old) with diagnostic uncertainty of asthma
INDEX TEST:	Combination of total IgE, FeNO and blood eosinophilia
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 X Inaccurate ○ Accurate ○ Very accurate ○ Varies ○ Don't know 	<p>Only one study assessing this question.</p> <p>The unique study assessing this question reported a sensitivity of 0.46 (95% CI: 0.37 to 0.52) and a specificity of 0.74 (95% CI: 0.64 to 0.79) for asthma diagnosis.</p> <p>Combining the three biomarkers did not increase the performance of the tests since the AUC remained at 0.6 (95 CI 0.56-0.64).</p> <p>Relying on the combination of T2 biomarkers (IgE, FeNO and eosinophilia) to make an asthma diagnosis in patients with suggestive symptoms lacks accuracy.</p>	<p>This observation also supports the concept that asthma may also be a non-T2 disease. The combination of these tests would not be helpful for non- T2 asthma, so it would not help ruling out asthma. Besides, the combination of the 3 biomarkers does not improve the diagnostic yield of each biomarker alone.</p>
Desirable Effects How substantial are the desirable anticipated effects?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Trivial <ul style="list-style-type: none"> Small Moderate Large Varies Don't know 	<p>The study by Nekoe et al. reported that in the clinical context of primary care (pre-test probability 30%), out of 1000 patients tested, 138 corresponded to true positives and 518 corresponded to true negatives. In secondary care (pre-test probability 50%), out of 1000 patients tested, 230 corresponded to true positives and 370 corresponded to true negatives.</p>	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> Large Moderate Small X Trivial <ul style="list-style-type: none"> Varies Don't know 	<p>The study by Nekoe et al. reported that in the clinical context of primary care (pre-test probability 30%), out of 1000 patients tested, 162 corresponded to false negatives and 182 corresponded to false positives. In secondary care (pre-test probability 50%), out of 1000 patients tested, 270 corresponded to false negatives and 130 corresponded to false positives.</p>	

Certainty of the evidence of test accuracy

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Very low <ul style="list-style-type: none"> Low Moderate High No included studies 	<p>Results limited to a one single retrospective cross-sectional study:</p> <p>The combination of IgE, blood eosinophilia and FeNO for asthma diagnosis showed a sensitivity of 0.46 (95% CI: 0.37 to 0.52) and a specificity of 0.74 (95% CI: 0.64 to 0.69) for asthma diagnosis (GRADE: ⊕⊕⊕○ moderate quality of evidence)</p> <p>Combining the three biomarkers did not increase the performance of the tests since the AUC remained at 0.6 (95 CI 0.56-0.64)</p>	

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
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<ul style="list-style-type: none"> ○ Very low ○ Low X Moderate ○ High ○ No included studies 	Results limited to a single one retrospective cross-sectional study with moderate quality of evidence.	The combination of the different T2 biomarkers (IgE, FeNO and blood eosinophilia) does not seem to increase the diagnostic likelihood of each test alone.
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 	Results limited to one single retrospective cross-sectional study with low quality of evidence. If positive, the management of asthma can be started, although no additional benefit of combining these 3 tests was observed in the study by Nekoe et al. Comparing to each test alone.	Useful when they are positive (high specificity), but not useful if they are negative; not useful to rule out asthma
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<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 	Based on the only study available, combining these tests do not provide additional benefits comparing to each test alone, however no undesirable effects were observed related to performing the tests.	There no harms related to these tests so, if they are performed and the tests are positive, then this is highly desirable. If negative, asthma should not be ruled out.
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 	We did not look for this evidence.	Comparing to the rest of the tests used for asthma diagnosis, costs of performing FeNO, IgE and blood eosinophilia do not exceed those required for the bronchodilator test or the bronchial provocation with methacholine.
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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 	We did not look for evidence on equity.	There not seem to be equity issues related to this test.

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 they are easy to perform, not time consuming, cheap and non-invasive biomarkers. In this context the panel considers that the tests are 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 	We did not look for evidence on feasibility.	The panel considers that given the availability and the acceptable cost of

<input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		performing IgE, blood eosinophilia and FeNO, there are not limitations identified related to feasibility.
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TYPE OF RECOMMENDATION

Strong recommendation against the intervention <input type="radio"/>	Conditional recommendation against the intervention <input checked="" type="radio"/>	Conditional recommendation for either the intervention or the comparison <input type="radio"/>	Conditional recommendation for the intervention <input type="radio"/>	Strong recommendation for the intervention <input type="radio"/>
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CONCLUSIONS

Recommendation

We suggest not using the combination of IgE, blood eosinophilia and FeNO for the diagnosis of asthma in adults (conditional recommendation, low quality of evidence).

Justification

Although a large study, the only study that met the criteria was a single-centre secondary care assessment. Combining blood eosinophils, total serum IgE and FeNO does not seem to improve diagnostic accuracy as compared to performing one single test. Further studies are needed, particularly those in primary care.

Subgroup considerations

The utility of the combination of the test would be limited to T2 asthma (eosinophilic asthma).

Research priorities

Further good quality studies should be performed to assess the utility of the combination of blood eosinophils, IgE and FeNO for asthma diagnosis.