Cohort Study
Potential PURL Review Form
PURL Jam Version

PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]

A. Citiation: Aaron SD, Vandemheen KL, FitzGerald JM, Ainslie M, Gupta S, Lemière C, Field SK, McIvor RA, Hernandez P, Mayers I, Mulpuru S, Alvarez GG, Pakhale S, Mallick R, Boulet LP; Canadian Respiratory Research Network. Reevaluation of Diagnosis in Adults With Physician-Diagnosed Asthma. JAMA. 2017 Jan 17;317(3):269-279. doi: 10.1001/jama.2016.19627. PubMed PMID: 28114551.
B. Link to PubMed Abstract: https://www.ncbi.nlm.nih.gov/pubmed/?term=28114551
C. First date published study available to readers:1/17/2017
D. PubMed ID: 28114551
E. Nominated By: Jim Stevermer
F. Institutional Affiliation of Nominator: University of Missouri
G. Date Nominated: 2/10/2017
H. Identified Through: POEMs
I. PURLs Editor Reviewing Nominated Potential PURL: Corey Lyon
J. Nomination Decision Date: 2/15/2017
K. Potential PURL Review Form (PPRF) Type: Cohort Study
L. Assigned Potential PURL Reviewer: Laura Morris
M. Reviewer Affiliation: University of Missouri
A. Abstract: IMPORTANCE:
Although asthma is a chronic disease, the expected rate of spontaneous remissions of adult asthma and the stability of diagnosis are unknown.

OBJECTIVE:
To determine whether a diagnosis of current asthma could be ruled out and asthma medications safely stopped in randomly selected adults with physician-diagnosed asthma.

DESIGN, SETTING, AND PARTICIPANTS:
A prospective, multicenter cohort study was conducted in 10 Canadian cities from January 2012 to February 2016. Random digit dialing was used to recruit adult participants who reported a history of physician-diagnosed asthma established within the past 5 years. Participants using long-term oral steroids and participants unable to be tested using spirometry were excluded. Information from the diagnosing physician was obtained to determine how the diagnosis of asthma was originally made in the community. Of 1026 potential participants who fulfilled eligibility criteria during telephone screening, 701 (68.3%) agreed to enter into the study. All participants were assessed with home peak flow and symptom monitoring, spirometry, and serial bronchial challenge tests, and those participants using daily asthma medications had their medications gradually tapered off over 4 study visits. Participants in whom a diagnosis of current asthma was ultimately ruled out were followed up clinically with repeated bronchial challenge tests over 1 year.

EXPOSURE:
Physician-diagnosed asthma established within the past 5 years.

MAIN OUTCOMES AND MEASURES:
The primary outcome was the proportion of participants in whom a diagnosis of current asthma was ruled out, defined as participants who exhibited no evidence of acute worsening of asthma symptoms, reversible airflow obstruction, or bronchial hyperresponsiveness after having all asthma medications tapered off and after a study pulmonologist established an alternative diagnosis. Secondary outcomes included the proportion with asthma ruled out after 12 months and the proportion who underwent an appropriate initial diagnostic workup for asthma in the community.

RESULTS:
Of 701 participants (mean [SD] age, 51 [16] years; 467 women [67%]), 613 completed the study and could be conclusively evaluated for a diagnosis of current asthma. Current asthma was ruled out in 203 of 613 study participants (33.1%; 95% CI, 29.4%-36.8%). Twelve participants (2.0%) were found to have serious cardiorespiratory conditions that had been previously misdiagnosed as asthma in the community. After an additional 12 months of follow-up, 181 participants (29.5%; 95% CI, 25.9%-33.1%) continued to exhibit no clinical or laboratory evidence of asthma. Participants in whom current asthma was ruled out, compared with those in whom it was confirmed, were less likely to have undergone testing for airflow limitation in the community at the time of initial diagnosis (43.8% vs 55.6%, respectively; absolute difference, 11.8%; 95% CI, 2.1%-21.5%).

CONCLUSIONS AND RELEVANCE:
Among adults with physician-diagnosed asthma, a current diagnosis of asthma could not be established in 33.1% who were not using daily asthma medications or had medications weaned. In patients such as these, reassessing the asthma diagnosis may be warranted.

B. Pending PURL Review Date**:** 1/31/2018

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]

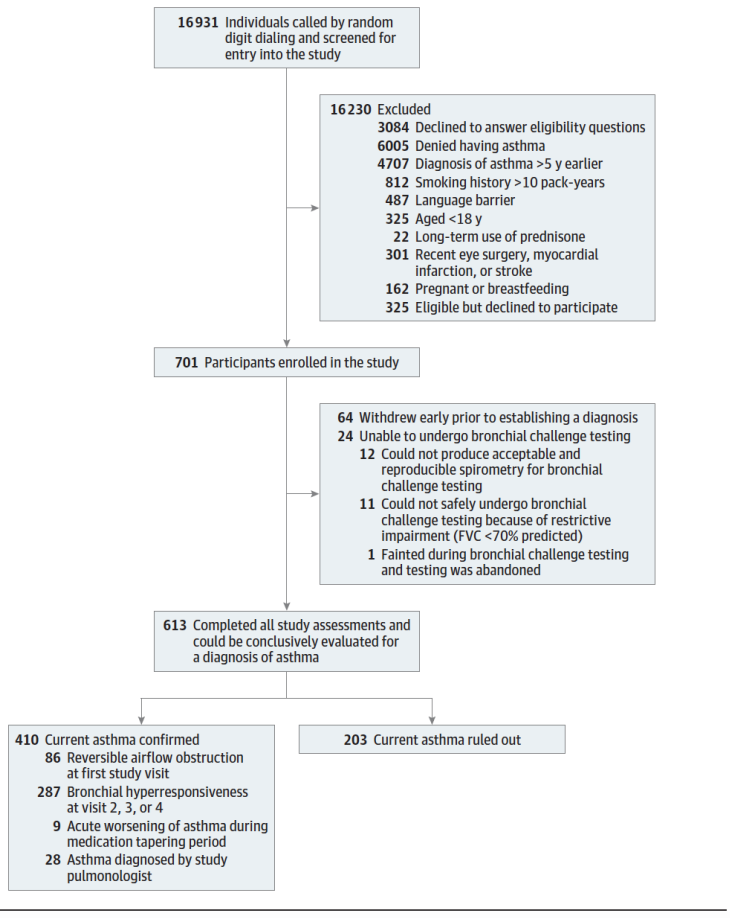
A. The study address an appropriate and clearly focused question. Yes & No Choose an item.

Comments: Appropriate- Yes- Newly diagnosed asthma in adults may not require continued treatment and may be an incorrect diagnosis.
Clearly focused- Yes- two main points. Patient with initial diagnosis without PFTs are more likely to have remission if retested. Weaning off meds is achievable for a large proportion of patients.

B. The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation. N/A or No Choose an item.
Comments: Cohort study looking at one group of patients
Did find differences between the groups
Type of physician who made diagnosis
Spirometry performed at time of diagnosis
Steroid use & Medication use
History of hypertension

C. The study indicates how many of the people asked to take part in it in each of the groups being studied. Yes Choose an item.
Comments: See Fig. 2

Figure 2. Recruitment of Study Participants and Study Outcomes



FVC indicates forced vital capacity.

D. The likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis. N/A or Yes Choose an item.
N/A Comments: The study does try to analyze the amount of misdiagnosis that is present.

E. What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed? 20% at initial screening declined enrollment and 13% dropped out after initial enrollment

F. Comparison is made between full participants and those lost to follow up, by exposure status. No Choose an item.
Comments: 18/231 patients tapered off meds did not attend follow-up appt. They were assessed by telephone and considered asymptomatic

Demographic information was not collected from 325 individuals who were eligible to enter the study but chose not to participate making a comparison impossible.

G. The outcomes are clearly defined. Yes Choose an item.
- Comments: Primary outcome- proportion of participants in whom a diagnosis of current asthma was ruled out
  - No evidence of acute worsening of symptoms
  - No reversible airflow obstruction
  - No bronchial hyperresponsiveness after having all asthma medications tapered off and having a pulmonologist establish a diagnosis
- Secondary outcomes
  - Proportion in whom asthma was rule out at 12 months
  - Proportion who underwent appropriate initial diagnostic workup

H. The assessment of outcome is made blind to exposure status. N/a Choose an item.
- Comments: The only blinding mentioned in the study was in regards to the assessment of how the initial diagnosis was established by the physician. Diagnostic tests were reviewed by pulmonologists who were blinded to the patient outcomes.
- It is not clear if the assessments performed during the study were blinded.

I. Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome. N/A Choose an item.
Comments: Not mentioned

J. What are the key findings of the study?
Adult onset asthma warrants reassessment as often medications can weaned and it is no longer active.
Objective tests such as PFTs should be used when possible when diagnosing asthma.

K. How was the study funded? Any conflicts of interest? Any reason to believe that the results may be influenced by other interests?
a. Grant Funding from the Canadian Institute of Health Research
b. Methapharm Inc. supplied provocholine
c. Trudell Medical International Inc supplied peak flow meters
d. ASDE Survey Sampler Inc organized the random digit dialing
e. The authors all had relationships with pharmaceutical companies. No clear conflicts.
f. No reason to believe results influenced by other interests.

SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

Citation Instructions: For up-to-date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS on editor & current year as publication year.

Example: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. {Insert date modified if given.} Accesses February 12, 2009. [whatever date PPRF reviewer did their search.}

For DynaMed, use the following style:
Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at http://www.DynamicMedical.com. Last updated February 4, 2009. {Insert date modified if given.} Accessed June 5, 2009. {search date}

A. DynaMed excerpts

National Heart, Lung, and Blood Institute severity classification for patients > 12 years old
classification of severity in stepwise management initially determined by patient's history

Components of Severity	Classification of Asthma Severity			
	Intermittent	**Persistent**		
		Mild	**Moderate**	**Severe**
Symptom frequency	≤ 2 days/week	> 2 days/week but not daily	Daily	Throughout the day
Nighttime awakenings	≤ 2 times/month	3-4 times/month	> once/week but not nightly	Often 7 times/week
Short-acting beta-2 agonists use for symptom control (not prevention of exercise-induced bronchospasm)	≤ 2 days/week	> 2 days/week but not daily	Daily	Several times daily
Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Lung function	Normal FEV_1 between exacerbations FEV_1 > 80% predicted FEV_1/FVC normal	FEV_1 > 80% predicted FEV_1/FVC normal	FEV_1 60%-80% predicted FEV_1/FVC reduced 5%	FEV_1 < 60% predicted FEV_1/FVC reduced > 5%
Exacerbations requiring oral systemic corticosteroids	0-1 yearly	≥ 2 times yearly		
	Consider severity and interval since last exacerbation; frequency and severity may fluctuate over time for patients in any severity category			

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

National Heart, Lung, and Blood Institute Severity Classification for Patients > 12 Years Old Not Currently Taking Long-term Control Medication:

a. Reference - National Asthma Education and Prevention Program Expert Panel Report 3 (EPR-3) guidelines for the diagnosis and management of asthma-summary report 2007 (J Allergy Clin Immunol 2007 Nov;120(5 Suppl):S94)

Testing overview:

- spirometry
  - should be obtained at time of initial assessment (NHLBI Evidence C) and at least every 1-2 years to assess maintenance of airway function (NHLBI Evidence B)
  - bronchial provocation with methacholine challenge test can be considered to diagnose airway hyperresponsiveness in patients with forced expiratory volume in 1 second (FEV_1) ≥ 65% predicted
- peak expiratory flow rate (PEFR) more useful for monitoring than diagnosis; long-term daily peak flow monitoring suggested if moderate or severe persistent asthma (NHLBI Evidence B) or history of severe exacerbations (NHLBI Evidence B)

Global Initiative for Asthma (GINA) suggested criteria for confirming variable expiratory airflow limitation[3]

Diagnostic Feature	Criteria for Making Diagnosis
○ Documented excessive variability in lung function* AND ○ Documented airflow limitation	○ More confident diagnosis the greater the variations or the more occasions excess variation seen ○ At least once during diagnostic process when FEV_1 low, confirm that FEV_1/FVC reduced (normally > 0.75-0.80 in adults)
Positive BD reversibility test* (more likely to be positive if BD medication withheld before test: SABA ≥ 4 hours, LABA ≥ 15 hours)	Increase in FEV_1 of > 12% and > 200 mL from baseline, 10-15 minutes after 200-400 mcg albuterol or equivalent (greater confidence if increase is > 15% and > 400 mL)
Excessive variability in twice-daily PEF over 2 weeks*	Average daily diurnal PEF variability > 10%**
Significant increase in lung function after 4 weeks of anti-inflammatory treatment	Increase in FEV_1 by > 12% and > 200 mL (or PEF*** by > 20%) from baseline after 4 weeks of treatment, outside respiratory infections
Positive exercise challenge test*	Fall in FEV_1 from baseline ≥ 20% with standard doses of methacholine or histamine, or ≥ 15% with standardized hyperventilation, hypertonic saline, or mannitol challenge.
Excessive variation in lung function between visits* (less reliable)	Variation in FEV_1 of > 12% and > 200 mL between visits, outside of respiratory infections
Variable respiratory symptoms but no variable airflow limitation	○ Repeat BD reversibility test again after withholding BD (SABA: 4 hours; LABA: 12+ hours) or during symptoms; if normal consider alternative diagnoses ○ If FEV_1 is > 70% predicted: consider stepping up controller treatment for 3 months then reassess symptoms and lung function; if no response, resume prior treatment and refer patient for diagnosis and investigation
Few respiratory symptoms, normal lung function, and no variable airflow limitation	○ Repeat BD reversibility test again after withholding BD (SABA: 4 hours; LABA: 12+ hours) or during symptoms; if normal consider alternative diagnoses ○ Consider stepping down controller treatment • Asthma confirmed if symptoms emerge and lung function falls; step up controller treatment to lowest previous effective dose • Consider ceasing controller and monitor patient for at least 12 months if no change in symptoms
Abbreviations: BD, bronchodilator; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LABA, long-acting $beta_2$-agonist; PEF, peak expiratory flow; SABA, short-acting $beta_2$-agonist. * These tests can be repeated during symptoms or in early morning. ** Daily diurnal PEF calculated from twice daily PEF as ([day's highest minus day's lowest]/mean of day's highest and lowest), and averaged over week. *** Use same meter each time, as PEF may vary by up to 20% between different meters; BD reversibility may be lost during severe	

Diagnostic Feature	Criteria for Making Diagnosis
exacerbations or viral infections.	
Diagnostic Criteria:	

bronchial provocation tests
- bronchial provocation may diagnose airway hyperresponsiveness
  - negative test may help to rule out asthma
  - positive test may indicate allergic rhinitis, cystic fibrosis, asthma, or other condition

B. DynaMed citation/ Asthma in Adults and adolescents. Topic Editor- Jonathan Ilowite, MD. In: DynaMed [database online]. Available at: www.DynamicMedical.com Last Updated 2018 Jan 3:Accessed 2018 Jan 30

C. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)
Intermittent asthma can result in widely spaced in time exacerbations with normal testing in the interim. In order to confirm asthma, there should be confirmed variability in lung function and airflow limitation.

D. UpToDate excerpts
Diagnosis based on history and clinical course — In some instances, the history and clinical course are strongly suggestive of asthma, and a treatment trial is initiated as part of the diagnostic process. The combination of a typical presentation (eg, repeated episodes of typical symptoms triggered by typical stimuli), musical wheezes on auscultation, and a prompt response to anti-asthma medication may be used to make a presumptive diagnosis, as might occur for new-onset asthma presenting in an acute care setting. However, we agree with the NAEPP guidelines that the clinical diagnosis of asthma should be validated with objective data, whenever possible. For patients with less typical or more persistent or refractory symptoms, formal spirometric data are essential to ensure that the correct diagnosis is identified [19].

The preferred approach to the diagnosis of asthma is the use of spirometry to identify reversible airflow obstruction. An obstructive pattern with an increase in FEV_1 of more than 12 percent from the baseline measurement, following administration of 2 to 4 puffs of a quick-acting bronchodilator, is suggestive of asthma, especially if post-bronchodilator spirometry is normal. (See 'Spirometry' above.)

●An alternative approach is to obtain serial measurements of FEV_1 or PEF over time at home or in the office. Patients can track the results in a peak flow diary). A variability of >10 percent that corresponds to symptoms is strongly suggestive of asthma. PEF measurement can be combined with a therapeutic trial of inhaled bronchodilator.

●Bronchoprovocation testing, such as with a methacholine, mannitol, or exercise challenge, is typically reserved for patients in whom the baseline spirometry is normal and the diagnosis remains uncertain.

●For clinical settings in which neither spirometry nor peak flow measurement is available, a diagnosis of probable asthma can be made based upon history alone, provided the patient has

typical symptoms that respond promptly and completely to therapy. History-based diagnosis is also appropriate for urgent care settings when patients respond to asthma therapies as expected. Peak flow measurements are appropriate in these office-based and urgent care settings to supplement history and exam.

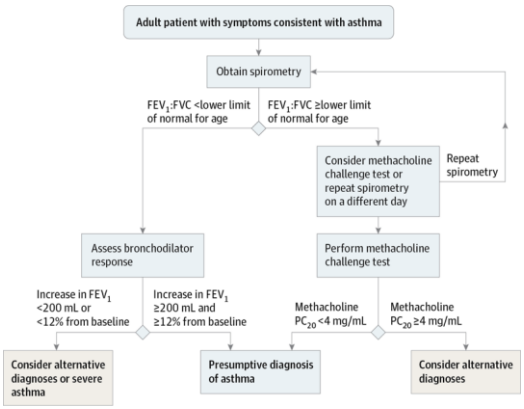
E. UpToDate citation/ Always use Basow DS as editor & current year as publication year. 2017 March 6. Diagnosis of asthma in adolescents and adults. Christopher H Fanta. In: UpToDate [database online]. Available at: http://www.uptodate.com. Last updated: 2018 Jan 30

Basow DS Editor 2017 March 6. Diagnosis of asthma in adolescents and adults. Christopher H Fanta. In: UpToDate [database online]. Available at: http://www.uptodate.com. Last updated: 2018 Jan 30

F. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)
History, exam findings and treatment response can all be highly suggestive of an asthma diagnosis and results in a probable diagnosis in settings where additional testing is not available. It is preferred to use spirometry or serial peak expiratory flows to identify a reversible airflow obstruction to confirm the diagnosis.

G. Other excerpts (USPSTF; other guidelines; etc.)
Michigan Guidelines- Detailed medical history and physical exam to determine that symptoms of recurrent episodes of airflow obstruction are present. Use Spirometry (FEV1, FEV6, FVC, FEV1/FVC) in all patients >5 of age to determine that airway obstruction is at least partially reversible [C] Consider alternative causes of airway obstruction

JAMA Review- The combination of asthma-like symptoms and β_2 agonist–reversible bronchial obstruction usually is sufficient to establish the diagnosis of asthma. Appropriate diagnostic testing should be conducted to confirm a diagnosis of asthma or suggest alternatives. …. Spirometry is the most important diagnostic procedure for evaluating airway obstruction and its reversibility. It should be performed in all patients in whom asthma is a diagnostic consideration.



Proposed Algorithm for Initial Diagnosis of Asthma

The first diagnostic test should be forced expiratory spirometry, categorized as obstructed (ratio of forced expiratory volume in first second of expiration [FEV_1] to forced vital capacity [FVC] less than lower limit of normal) or not obstructed. If airway obstruction is present, a bronchodilator response following 2 to 4 puffs of short-acting β_2-agonist should be determined. Fixed or partially reversible airway obstruction suggests alternative diagnoses, although severe asthma may be present. PC_{20} indicates the methacholine concentration required to achieve a 20% decrease in FEV_1.

H. Citations for other excerpts

Michigan Quality Improvement Consortium (MQIC) guidelines 2016
http://www.mqic.org/pdf/mqic%5Fgeneral%5Fprinciples%5Ffor%5Fthe%5Fdiagnosis%5Fand%5Fmanagement%5Fof%5Fasthma%5Fcpg.pdf

McCracken JL, Veeranki SP, Ameredes BT, Calhoun WJ. Diagnosis and Management of Asthma in Adults A Review. *JAMA.* 2017;318(3):279–290. doi:10.1001/jama.2017.8372

I. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)
Michigan Guidelines- Level C evidence that spirometry should be used in all patients >5 yo to determine reversible airway obstruction in addition to history and physical exam in the diagnosis of asthma.

JAMA review- Asthma like symptoms and β_2 agonist–reversible bronchial obstruction usually is sufficient to establish the diagnosis of asthma . Spirometry is the most important diagnostic procedure for evaluating aieway obstruction and reversibility and should be performed in all patients in whom asthma is diagnostic consideration.

SECTION 4: Conclusions
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

A. **Validity**: Are the findings scientifically valid? 3Choose an item.

B. If **A** was coded 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?

C. **Relevance**: Is the topic relevant to the practice of family medicine and primary care practice, including outpatient, inpatient, obstetrics, emergency and long-term care? Are the patients being studied sufficiently similar to patients cared for in family medicine and primary care in the US such that results can be generalized? 3
Choose an item.

D. If **C** was coded 4, 5, 6, or 7, please provide an explanation.

E. **Practice changing potential**: If the findings of the study are both valid and relevant, are they not a currently widely accepted recommendation among family physicians and primary care clinicians for whom the recommendation is relevant to their patient care? Or are the findings likely to be a meaningful variation regarding awareness and acceptance of the recommendation? 3
Choose an item.

F. If **E** was coded as 1, 2, 3, or4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit. When making an initial diagnosis of asthma in an adult it is useful to get objective testing such as PFTs. In adults with recently diagnosed asthma it is safe to wean medications and reconsider the diagnosis.

G. **Applicability to a Family Medical Care Setting**:
Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc.), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, education or counseling a patient; or creating a system for implementing an intervention? 2 Choose an item.

H. If **G** was coded as a 4, 5, 6, or 7, please explain.

I. **Immediacy of Implementation**:
Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug, or other essentials available on the market? 3 Choose an item.

J. If **I** was coded 4, 5, 6, or 7,please explain why.

K. **Clinically meaningful outcomes or patient oriented outcomes**:
Do the expected benefits outweigh the expected harms? Are the outcomes patient oriented (as opposed to disease oriented)? Are the measured outcomes, if true, clinically meaningful from a patient perspective? 3
Choose an item.

L. If **K** was coded 4, 5, 6, or 7 please explain why.

M. In your opinion, is this a pending PURL? 3 Choose an item.

1. Valid: Strong internal scientific validity; the findings appear to be true.
2. Relevant: Relevant to the practice of family medicine.
3. Practice Changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.
4. Applicability in medical setting.
5. Immediacy of implementation

N. Comments on your response for question M

Validity- Large number of study participants and well designed study
Relevant- it is relevant to EM and FM
Practice changing- Physicians should be ordering objective testing at diagnosis and attempt to wean patients off meds in recently diagnosed asthma
Applicability- Easy to implement in office setting – medication review and ordering of PFTs
Immediacy- Providers would easily implement within already existing office visits for asthma follow-up or well visits.