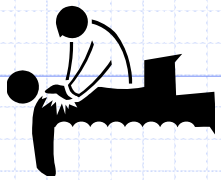
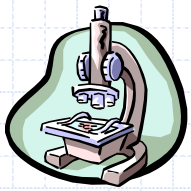
Diagnostic research designs: an introductory overview





Madhukar Pai, MD, PhD
Assistant Professor of Epidemiology, McGill University
Montreal, Canada

Email: madhukar.pai@mcgill.ca

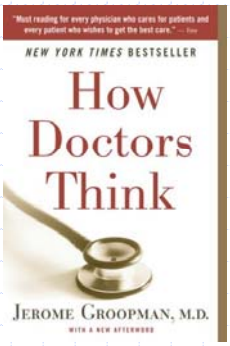
Approaches to Diagnosis

Pattern recognition	Probabilistic diagnostic reasoning
See it and recognize disorder	Clinical assessment generates pretest probability
↓	↓
Compare posttest probability with thresholds	New information generates posttest probability
(usually pattern recognition implies probability near 100% and so above threshold)	(may be interative)
	↓
	Compare posttest probability with thresholds

Source: Guyatt G, Rennie D, Meade MO, Cook DJ: *Users' Guides to the Medical Literature: A Manual for Evidence-Based Practice*, 2nd Edition: http://www.jamaevidence.com

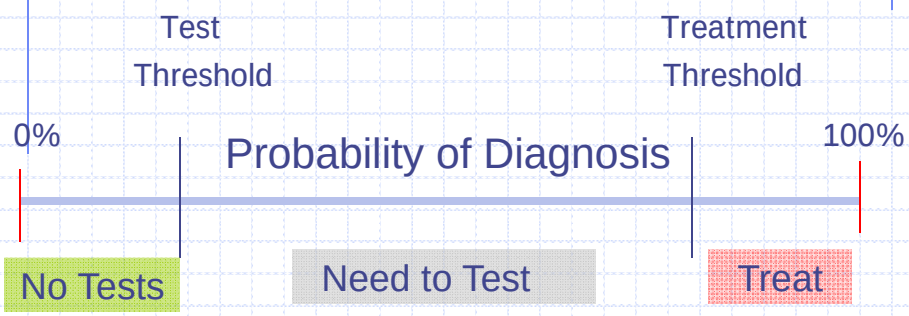
Misdiagnosis is common!

- Most misguided care results from thinking errors rather than technical mistakes.
- Major thinking traps: "three As"
  - Anchoring
    - Shortcut in thinking when a person doesn't consider multiple possibilities but quickly latches on to a single one.
  - Availability
    - Tendency to judge the likelihood of an event by the ease with which relevant examples come to mind.
  - Attribution
    - Based on stereotypes that are based on someone's appearance, emotional state or circumstances
- Key question to avoid these traps: "What else can it be?"

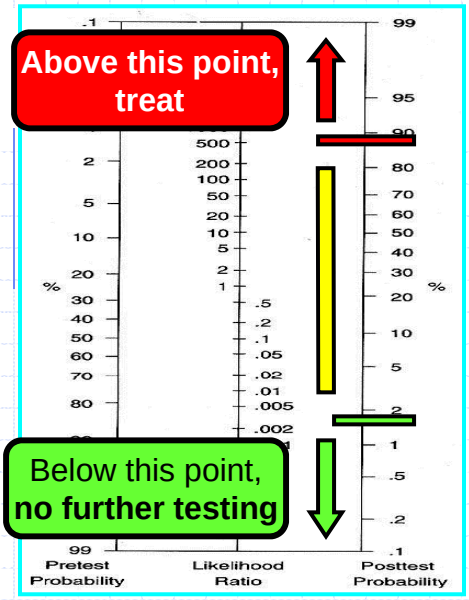


"Usually doctors are right, but conservatively about 15 percent of all people are misdiagnosed. Some experts think it's as high as 20 to 25 percent," - Groopman

Process of diagnosis: all about probability and decision making under uncertainty!



Thresholds for decision-making: when will you stop investigating? when will you test further? when will you rule out disease?

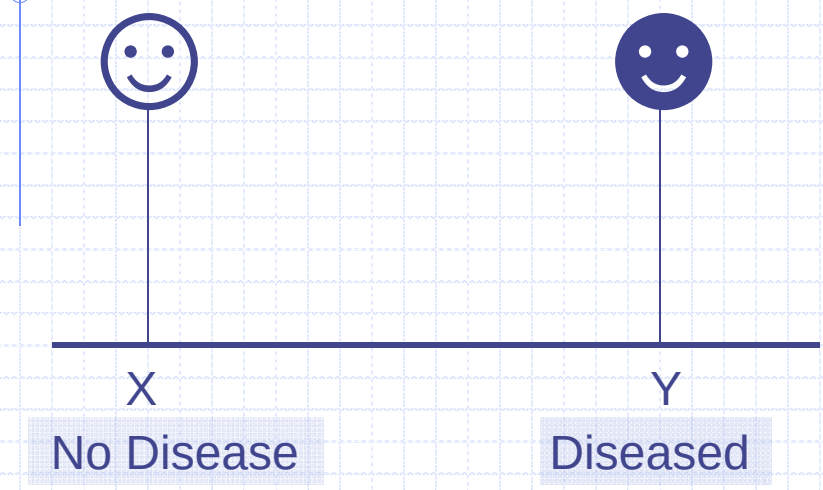


Disease ruled IN

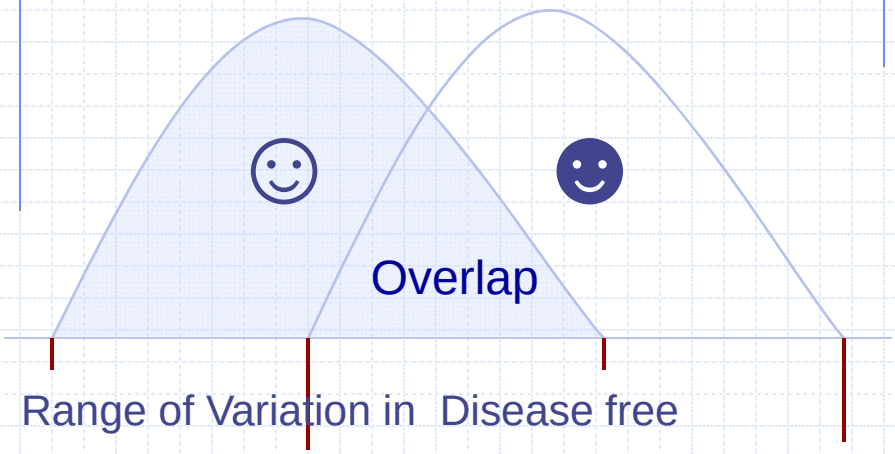
Disease not ruled in or out

Disease ruled OUT

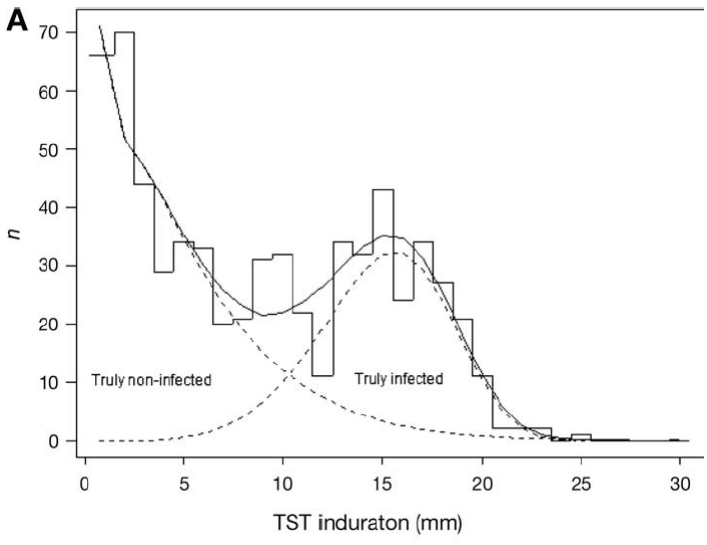
The Perfect Diagnostic Test



Variations In Diagnostic Tests



Example: TST distribution



Pai M et al. ITJLD 2008

There is no perfect test!

Thomas Bayes

Thomas Bayes (The correct identification of this portrait has been [1] questioned.)

Born	c. 1702 London
Died	April 17th 1761 Tunbridge Wells
Nationality	British

LII. *An Essay towards solving a Problem in the Doctrine of Chances. By the late Rev. Mr.* Bayes, *communicated by Mr.* Price, *in a letter to* John Canton, *M. A. and F. R. S.*

Dear Sir,

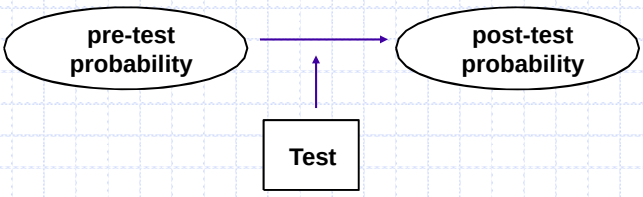
Read Dec. 23, 1763. I now send you an essay which I have found among the papers of our deceased friend Mr. Bayes, and which, in my opinion, has great merit, and well deserves to be preserved. Experimental philosophy, you will find, is nearly interested in the subject of it; and on this account there seems to be particular reason for thinking that a communication of it to the Royal Society cannot be improper.

He had, you know, the honour of being a member of that illustrious Society, and was much esteemed by many as a very able mathematician. In an introduction which he has writ to this Essay, he says, that his design at first in thinking on the subject of it was, to find out a method by which we might judge concerning the probability that an event has to happen, in given circumstances, upon supposition that we know nothing concerning it but that, under the same circumstances, it has happened a certain number of times, and failed a certain other number of times. He adds, that he soon perceived that it would not be very difficult to do this, provided some rule could be found, according to which we ought to estimate the chance that the probability for the happening of an event perfectly unknown, should lie between any two named degrees of prob-

All we can hope to do is increase or decrease probabilities, and Bayes' theorem helps with this process

Bayes' theory

- Bayes' Theorem is a simple mathematical formula used for calculating conditional probabilities
- every test is done with a certain probability of disease - degree of suspicion [pre-test or prior probability]
- the probability of disease after the test result is the post-test or posterior probability



Post-test odds = Pre-test odds x Likelihood ratio

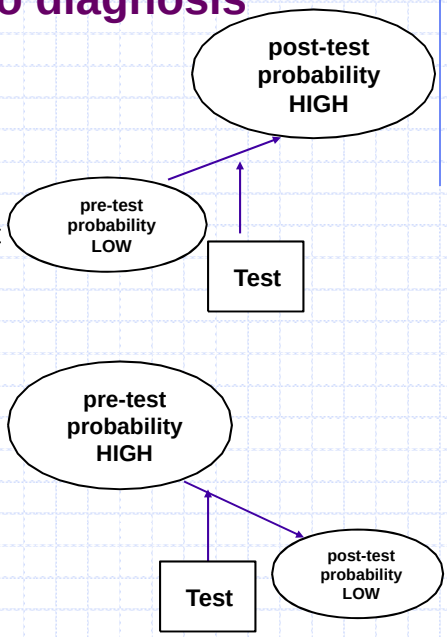
The most simplistic way of explaining Bayes' theorem

What you thought before + New information = What you think now

Newman T, Kohn MA. Evidence-based diagnosis. 2009, Cambridge Univ Press

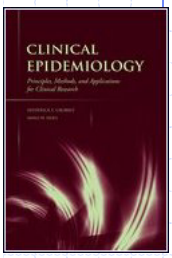
Bayesian approach to diagnosis

- An accurate test will help reduce uncertainty
- The pre-test probability is revised using test result to get the post-test probability
- Tests that produce the biggest changes from pretest to post-test probabilities are most useful in clinical practice [very large or very small likelihood ratios]
- LR also called "Bayes Factor"



The diagnostic process is Bayesian, probabilistic, multivariable and sequential

1. A diagnosis starts with a patient presenting a complaint (symptom and/or sign) suggestive of a certain disease to be diagnosed.
2. The subsequent work-up is a multivariable process. It involves multiple diagnostic determinants (tests) that are applied in a logical order: from age, gender, medical history, and signs and symptoms, to more complicated, invasive, and costly tests.
3. Setting or ruling out a diagnosis is a probabilistic action in which the probability of the presence or absence of the disease is central. This probability is continuously updated based on subsequent diagnostic test results.
4. The true diagnostic value of a test is determined by the extent to which it provides diagnostic information beyond earlier tests, that is, materially changes the probability estimation of disease presence based on previous test results.
5. The goal of the diagnostic process is to eventually rule in or out the disease with enough confidence to take clinical decisions. This requires precise estimates of the probability of the presence of the target disease(s).



Moons KGM. In: Grobbee & Hoes. Clinical Epidemiology. 2009

Diagnosis Vs Screening

- A diagnostic test is done on sick people
  - patient presents with symptoms
  - pre-test probability of disease is high (i.e. disease prevalence is high)
- A screening test is usually done on asymptomatic, apparently healthy people
  - healthy people are encouraged to get screened
  - pre-test probability of disease is low (i.e. disease prevalence is low)

Diagnosis vs. prediction

- Diagnosis:
  - Disease has already occurred and we are trying to detect its presence
- Prognosis:
  - Disease has not occurred and we want to know who is most likely to develop the disease
- Both are amenable to multivariable approaches and prediction models
- They are often mixed up
  - Sometimes a diagnostic test itself can be used to predict future outcomes (e.g. PSA)

PERSPECTIVE | Annals of Internal Medicine

Against Diagnosis

Andrew J. Vickers, PhD; Ethan Basch, MD; and Michael W. Kattan, PhD

The act of diagnosis requires that patients be placed in a binary category of either having or not having a certain disease. Accordingly, the diseases of particular concern for industrialized countries—such as type 2 diabetes, obesity, or depression—require that a somewhat arbitrary cut-point be chosen on a continuous scale of measurement (for example, a fasting glucose level >6.9 mmol/L [>125 mg/dL] for type 2 diabetes). These cut-points do not adequately reflect disease biology, may inappropriately treat patients on either side of the cut-point as 2 homogenous risk groups, fail to incorporate other risk factors, and are invariable to patient preference. This article discusses risk prediction as an alternative to diagnosis: Patient risk factors (blood pressure, age) are combined into a single statistical model (risk for a cardiovascular event within 10 years) and the results are used in shared decision making about possible treatments. The authors compare and contrast the diagnostic and risk prediction approaches and attempt to identify the types of medical problem to which each is best suited.

Ann Intern Med. 2008;149:200-203. www.annals.org
For author affiliations, see end of text.

Table. Comparison of Typical Features of Diagnostic and Risk Prediction Approaches

Variable	Diagnosis	Risk Prediction
Approach	Patients are given a diagnosis: Either they have the disease or they do not	Patients are given a probability of a future event
Example	Syphilitic hepatitis	Cardiovascular event within 10 years
Lesion	Unambiguous	Nonexistent or equivocal
Example	Torn aorta	Depression
Treatment effectiveness	Often highly effective	Helpful, but patients may have event with treatment or avoid the event even if untreated
Example	Antibiotics for syphilis	Statins for high cholesterol level
Course of treatment	Dictated by diagnosis	Open to discussion
Example	Surgical treatment of a torn aorta	Treatment of early-stage prostate cancer
Patient preference	Generally of minor importance	Often of major importance
Example	Antibiotics for syphilis	Treatment of early-stage prostate cancer
Symptoms	Patient has distressing symptoms	Patient is often asymptomatic: Disorder is a risk factor for a future event
Example	Syphilitic hepatitis	Hyperlipidemia

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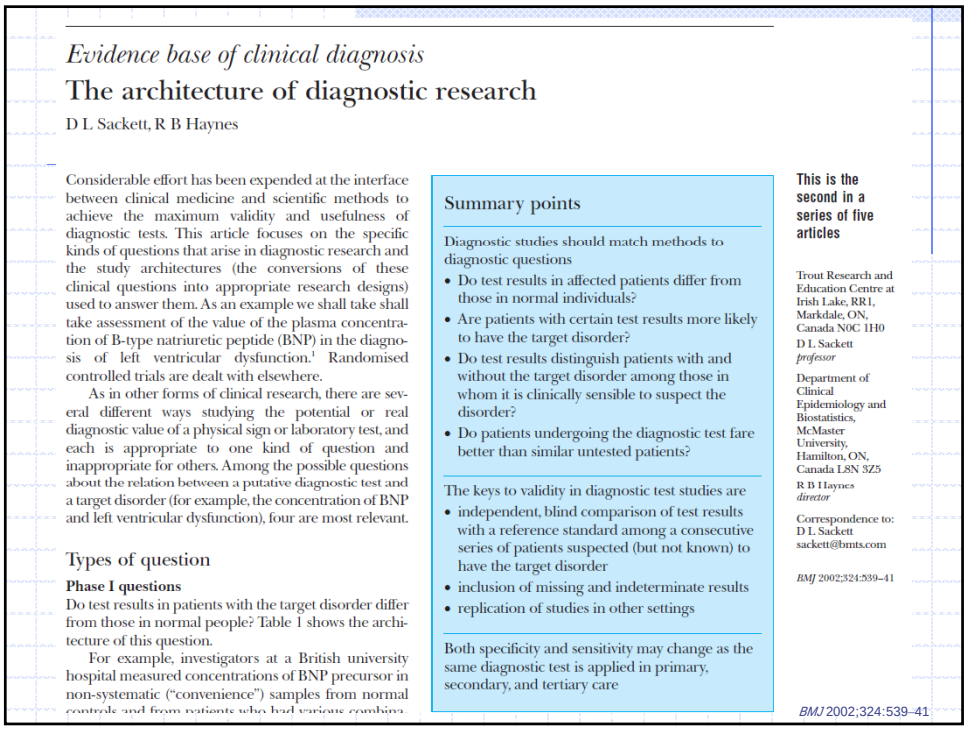
Types of diagnostic study designs (Phased approach)

Phases in intervention/drug trials

- **Phase I:** Researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.
- **Phase II:** The drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.
- **Phase III:** The drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.
- **Phase IV:** Studies are done after the drug or treatment has been marketed to gather information on the drug's effect in various populations and any side effects associated with long-term use.



Evidence base of clinical diagnosis

The architecture of diagnostic research

D L Sackett, R B Haynes

Considerable effort has been expended at the interface between clinical medicine and scientific methods to achieve the maximum validity and usefulness of diagnostic tests. This article focuses on the specific kinds of questions that arise in diagnostic research and the study architectures (the conversions of these clinical questions into appropriate research designs) used to answer them. As an example we shall take shall take assessment of the value of the plasma concentration of B-type natriuretic peptide (BNP) in the diagnosis of left ventricular dysfunction.[1] Randomised controlled trials are dealt with elsewhere.

As in other forms of clinical research, there are several different ways studying the potential or real diagnostic value of a physical sign or laboratory test, and each is appropriate to one kind of question and inappropriate for others. Among the possible questions about the relation between a putative diagnostic test and a target disorder (for example, the concentration of BNP and left ventricular dysfunction), four are most relevant.

Types of question

Phase I questions

Do test results in patients with the target disorder differ from those in normal people? Table 1 shows the architecture of this question.

For example, investigators at a British university hospital measured concentrations of BNP precursor in non-systematic ("convenience") samples from normal controls and from patients who had various combina-

Summary points

Diagnostic studies should match methods to diagnostic questions

- Do test results in affected patients differ from those in normal individuals?
- Are patients with certain test results more likely to have the target disorder?
- Do test results distinguish patients with and without the target disorder among those in whom it is clinically sensible to suspect the disorder?
- Do patients undergoing the diagnostic test fare better than similar untested patients?

The keys to validity in diagnostic test studies are

- independent, blind comparison of test results with a reference standard among a consecutive series of patients suspected (but not known) to have the target disorder
- inclusion of missing and indeterminate results
- replication of studies in other settings

Both specificity and sensitivity may change as the same diagnostic test is applied in primary, secondary, and tertiary care

This is the second in a series of five articles

Trout Research and Education Centre at Irish Lake, RR1, Markdale, ON, Canada N0C 1H0
D L Sackett
professor

Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada L8N 3Z5
R B Haynes
director

Correspondence to:
D L Sackett
sackett@bmts.com

BMJ 2002;324:539–41

Phase I to IV diagnostic studies

- **Phase I questions**
  - Do test results in patients with the target disorder differ from those in normal people?

Table 1 Answering a phase I question: do patients with left ventricular dysfunction have higher concentrations of B-type natriuretic peptide (BNP) precursor than normal individuals?

	Patients known to have disorder	Normal controls
Median (range) concentration of BNP precursor (pg/ml)	493.5 (248.9-909.0)	129.4 (53.6-159.7)

BMJ 2002;324:539–41

Phase I to IV diagnostic studies

- **Phase II questions**
  - Are patients with certain test results more likely to have the target disorder than patients with other test results?

Table 2 Answering a phase II question: are patients with higher concentrations of B-type natriuretic peptide (BNP) more likely to have left ventricular dysfunction than patients with lower concentrations?

	Patients known to have target disorder	Normal controls
High BNP concentration	39	2
Normal BNP concentration	1	25

Test characteristics (95% CI):
Sensitivity=98% (87% to 100%)
Specificity=92% (77% to 98%)
Positive predictive value=95% (84% to 99%)
Negative predictive value=96% (81% to 100%)
Likelihood ratio for an abnormal test result=13 (3.5 to 50.0)
Likelihood ratio for a normal test result=0.03 (0.0003 to 0.19)

BMJ 2002;324:539–41

Phase I to IV diagnostic studies

- **Phase III questions**
  - Does the test result distinguish patients with and without the target disorder among patients in whom it is clinically reasonable to suspect that the disease is present?

Table 3 Answering a phase III question: among patients in whom it is clinically sensible to suspect left ventricular dysfunction (LVD), does the concentration of B-type natriuretic peptide (BNP) distinguish patients with and without left ventricular dysfunction?

	Patients with LVD on echocardiography	Patients with normal results on echocardiography
Concentration of BNP:		
High (>17.9 pg/ml)	35	57
Normal (<18 pg/ml)	5	29
Prevalence (pretest probability) of LVD	40/126=32%	

Test characteristics (95% CI):
Sensitivity=88% (74% to 94%)
Specificity=34% (25% to 44%)
Positive predictive value=38% (29% to 48%)
Negative predictive value=85% (70% to 94%)
Likelihood ratio for an abnormal test result=1.3 (1.1 to 1.6)
Likelihood ratio for a normal test result=0.4 (0.2 to 0.9)

BMJ 2002;324:539–41

Phase I to IV diagnostic studies

- **Phase IV questions**
  - Do patients who undergo this diagnostic test fare better (in their ultimate health outcomes) than similar patients who are not tested?

BMJ 2002;324:539–41

Phases in technology development

Freedman et al. 1987	Thornbury and Fryback, 1992	Pepe, 2005
I. Feasibility, promise	I. Technical efficacy	I. Preclinical exploratory
II. Studies of diagnostic accuracy	II. Diagnostic accuracy efficacy	II. Clinical assay and validation
III. Studies of clinical value	III. Diagnostic thinking efficacy	III. Retrospective longitudinal
IV. Studies for monitoring routine use	IV. Therapeutic efficacy	IV. Prospective screening
	V. Patient outcome efficacy	V. Disease control
	VI. Societal efficacy	

Redundancy of Single Diagnostic Test Evaluation

Karel G.M. Moons,[1,2,3] Gerri-Anne van Es,[4] Bowine C. Michel,[5] Harry R. Büller,[6] J. Dik F. Habbema,[3] and Diederick E. Grobbee[1]

Moons et al. Epidemiology 1999

Diagnostic research

Diagnostic studies as multivariable, prediction research

K G M Moons, D E Grobbee

Patient outcomes in diagnostic research

Moons et al. JECH 2002

Opinion

Test Research versus Diagnostic Research

Moons et al. Clin Chem 2004

Multivariable approach

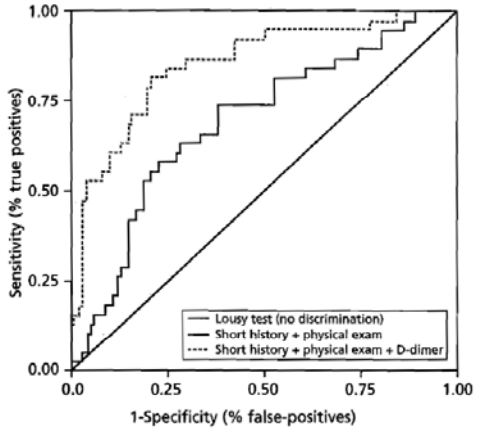


FIGURE 3.3 Example of an ROC curve of the reduced multivariable logistic regression model, including the same six determinants as in Figure 3.2. The ROC area of the "reduced history + physical model" (red) was 0.70 (95% confidence interval [CI], 0.66–0.74) and of the same model added with the D-dimer assay (green) 0.84 (95% CI, 0.80–0.88).

Key outcome here is what is the added value of a new test, beyond all the prior tests that may have been done (including history/physical)

Moons KGM. In: Grobbee & Hoes. Clinical Epidemiology. 2009

AHRQ EFFECTIVE HEALTH CARE PROGRAM WHITE PAPER SERIES

Proposals for a Phased Evaluation of Medical Tests

Jeroen G. Lijmer, MD, PhD, Mariska Leeflang, PhD, Patrick M. M. Bossuyt, PhD

Background. *In drug development, a 4-phase hierarchical model for the clinical evaluation of new pharmaceuticals is well known. Several comparable phased evaluation schemes have been proposed for medical tests.* ***Purpose.*** *To perform a systematic search of the literature, a synthesis, and a critical review of phased evaluation schemes for medical tests.* ***Data Sources.*** *Literature databases of Medline, Web of Science, and Embase.* ***Study Selection and Data Extraction.*** *Two authors separately evaluated potentially eligible papers and independently extracted data.* ***Results.*** *We identified 19 schemes, published between 1978 and 2007. Despite their variability, these models show substantial similarity. Common phases are evaluations of technical efficacy, diagnostic accuracy, diagnostic thinking efficacy, therapeutic efficacy, patient outcome, and societal aspects.* ***Conclusions.*** *The evaluation frameworks can be useful to distinguish between study types, but they cannot be seen as a necessary sequence of evaluations. The evaluation of tests is most likely not a linear but a cyclic and repetitive process.* ***Key words:*** *medical tests; biomarkers; test evaluation; medical technology assessment.* ***(Med Decis Making. 2009;29:E13–E21)***

Phased evaluation of medical tests

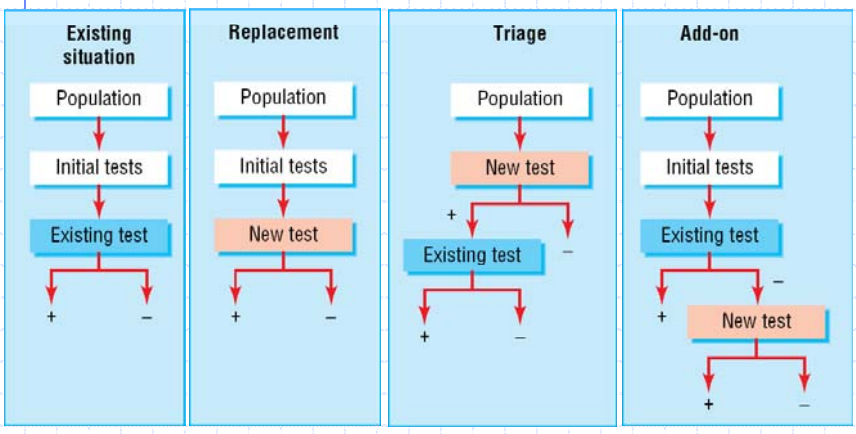
Levels/Phases
Technical efficacy
Intended use
Diagnostic accuracy
Usual range
Subgroups
Clinical population
Diagnostic thinking efficacy
Therapeutic efficacy
Patient outcome efficacy
Societal efficacy

Proposals for a Phased Evaluation of Medical Tests

Jeroen G. Lijmer, MD, PhD, Mariska Leeflang, PhD, Patrick M. M. Bossuyt, PhD

Med Desic Making 2009

Design is often decided by: what is the real purpose of the test?



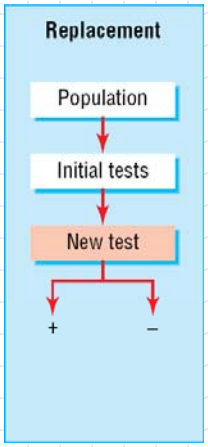
Bossuyt, BMJ, 2006

Approach to follow

- What is the current situation?
  - Setting, Patients, Prior testing, consequences
- What will the new test / strategy add?
- How may the (which?) outcomes change?
- What type of evidence is needed?

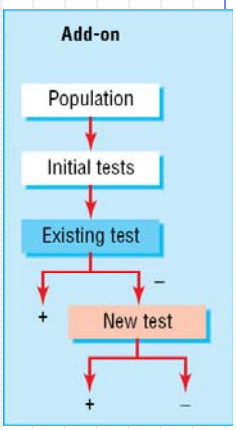
Replacement

- No change in consequences for TP, FP, FN, TN
- Accuracy may be enough (preferably paired data)
- Other info needed: costs, safety, burden, indeterminate results...



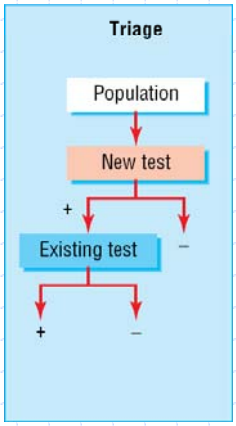
Add on

- Potential change in consequences, also extra numbers
  (either extra positives or extra negatives)
- Extra testing: extra time, burden
- Other info needed: costs, safety, burden, indeterminate results...
- Effect of change in consequences



Triage

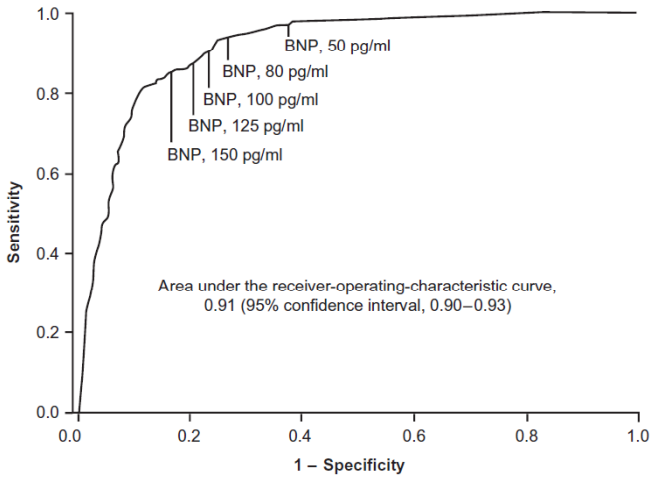
- May result in a completely different pathway and different population
- Accuracy will not be enough
- Other info needed: costs, safety, burden, indeterminate results...
- Advantage of early diagnosis?



Key issue to appreciate:

Accuracy may or may not result in clinical impact (on patient outcomes)

Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure



Maisel et al, *N Engl J Med.* 2002 Jul 18;**347**(3):

Annals of Internal Medicine | ARTICLE

B-Type Natriuretic Peptide Testing, Clinical Outcomes, and Health Services Use in Emergency Department Patients With Dyspnea

A Randomized Trial

Hans-Gerhard Schneider, MBBS, MD; Louisa Lam, MPH; Amaali Lokuge, MBBS; Henry Krum, MBBS, PhD; Matthew T. Naughton, MBBS; Pieter De Villiers Smit, MBBS; Adam Bystrzycki, MBBS; David Eccleston, MBBS, PhD; Jacob Federman, MBBS; Genevieve Flannery, MBBS; and Peter Cameron, MBBS, MD

Background: B-type natriuretic peptide (BNP) is used to diagnose heart failure, but the effects of using the test on all dyspneic patients is uncertain.

Objective: To assess whether BNP testing alters clinical outcomes and health services use of acutely dyspneic patients.

Design: Randomized, single-blind study. Patients were assigned to a treatment group through randomized numbers in a sealed envelope. Patients were blinded to the intervention, but clinicians and those who assessed trial outcomes were not.

Setting: 2 Australian teaching hospital emergency departments.

Patients: 612 consecutive patients who presented with acute severe dyspnea from August 2005 to March 2007.

Intervention: BNP testing (n = 306) or no testing (n = 306).

Measurements: Admission rates, length of stay, and emergency department medications (primary outcomes); mortality and readmission rates (secondary outcomes).

Results: There were no between-group differences in hospital admission rates (85.6% [BNP group] vs. 86.6% [control group]; difference, −1.0 percentage point [95% CI, −6.5 to 4.5 percentage points]; P = 0.73), length of admission (median, 4.4 days [interquartile range, 2 to 9 days] vs. 5.0 days [interquartile range, 2 to 9 days]; P = 0.94), or management of patients in the emergency department. Test discrimination was good (area under the receiver-operating characteristic curve, 0.87 [CI, 0.83 to 0.91]). Adverse events were not measured.

Limitation: Most patients were very short of breath and required hospitalization; the findings might not apply for evaluating patients with milder degrees of breathlessness.

Conclusion: Measurement of BNP in all emergency department patients with severe shortness of breath had no apparent effects on clinical outcomes or use of health services. The findings do not support routine use of BNP testing in all severely dyspneic patients in the emergency department.

Primary Funding Source: Janssen-Cilag.

Ann Intern Med. 2009;150:365-371. www.annals.org
For author affiliations, see end of text.
ClinicalTrials.gov registration number: NCT00163709.

OPEN ACCESS Freely available online | PLoS one

Evaluation of Diagnostic Accuracy, Feasibility and Client Preference for Rapid Oral Fluid-Based Diagnosis of HIV Infection in Rural India

Nitika Pant Pai[1]*, Rajnish Joshi[2], Sandeep Dogra[3], Bharati Taksande[2], S. P. Kalantri[2], Madhukar Pai[4], Pratibha Narang[2], Jacqueline P. Tulsky[5], Arthur L. Reingold[6]

1 Immunodeficiency Service, Montreal Chest Institute, McGill University Health Center, Montreal, Canada, 2 Mahatma Gandhi Institute of Medical Sciences, Sevagram, Maharashtra, India, 3 Acharya Shri Chander College of Medical Sciences, Jammu, India, 4 Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Canada, 5 Department of Internal Medicine, University of California at San Francisco, San Francisco, California, United States of America, 6 Division of Epidemiology, University of California at Berkeley, Berkeley, California, United States of America

Background. Oral fluid-based rapid tests are promising for improving HIV diagnosis and screening. However, recent reports from the United States of false-positive results with the oral OraQuick® ADVANCE HIV1/2 test have raised concerns about their performance in routine practice. We report a field evaluation of the diagnostic accuracy, client preference, and feasibility for the oral fluid-based OraQuick® Rapid HIV1/2 test in a rural hospital in India. ***Methodology/Principal Findings.*** A cross-sectional, hospital-based study was conducted in 450 consenting participants with suspected HIV infection in rural India. The objectives were to evaluate performance, client preference and feasibility of the OraQuick® Rapid HIV-1/2 tests. Two Oraquick® Rapid HIV1/2 tests (oral fluid and finger stick) were administered in parallel with confirmatory ELISA/Western Blot (reference standard). Pre- and post-test counseling and face to face interviews were conducted to determine client preference. Of the 450 participants, 146 were deemed to be HIV sero-positive using the reference standard (seropositivity rate of 32% (95% confidence interval [CI] 28%, 37%)). The OraQuick test on oral fluid specimens had better performance with a sensitivity of 100% (95% CI 98, 100) and a specificity of 100% (95% CI 99, 100), as compared to the OraQuick test on finger stick specimens with a sensitivity of 100% (95% CI 98, 100), and a specificity of 99.7% (95% CI 98.4, 99.9). The OraQuick oral fluid-based test was preferred by 87% of the participants for first time testing and 60% of the participants for repeat testing. ***Conclusion/Significance.*** In a rural Indian hospital setting, the OraQuick® Rapid- HIV1/2 test was found to be highly accurate. The oral fluid-based test performed marginally better than the finger stick test. The oral OraQuick test was highly preferred by participants. In the context of global efforts to scale-up HIV testing, our data suggest that oral fluid-based rapid HIV testing may work well in rural, resource-limited settings.

Citation: Pant Pai N, Joshi R, Dogra S, Taksande B, Kalantri SP, et al (2007) Evaluation of Diagnostic Accuracy, Feasibility and Client Preference for Rapid Oral Fluid-Based Diagnosis of HIV Infection in Rural India. PLoS ONE 2(4): e367. doi:10.1371/journal.pone.0000367

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Impact of Round-the-Clock, Rapid Oral Fluid HIV Testing of Women in Labor in Rural India

Nitika Pant Pai[1*], Ritu Barick[2], Jacqueline P. Tulsky[3], Poonam V. Shivkumar[2], Deborah Cohan[3], Shriprakash Kalantri[2], Madhukar Pai[4], Marina B. Klein[1], Shakuntala Chhabra[2]

1 Division of Infectious Diseases and Immunodeficiency Service, Montreal Chest Institute, McGill University Health Center, Montreal, Canada, 2 Mahatma Gandhi Institute of Medical Sciences, Sevagram, Wardha, Maharashtra, India, 3 Positive Health Program, Division of Internal Medicine, University of California San Francisco, San Francisco, California, United States of America, 4 Department of Epidemiology and Biostatistics, McGill University, Montreal, Canada

Methods and Findings

After they provided written informed consent, women admitted to the labor ward of a rural teaching hospital in India were offered two rapid tests on oral fluid and finger-stick specimens (OraQuick Rapid HIV-1/HIV-2 tests, OraSure Technologies). Simultaneously, venous blood was drawn for conventional HIV ELISA testing. Western blot tests were performed for confirmatory testing if women were positive by both rapid tests and dual ELISA, or where test results were discordant. Round-the-clock (24 h, 7 d/wk) abbreviated prepartum and extended postpartum counseling sessions were offered as part of the testing strategy. HIV-positive women were administered PMTCT interventions. Of 1,252 eligible women (age range 18 y to 38 y) approached for consent over a 9 mo period in 2006, 1,222 (98%) accepted HIV testing in the labor ward. Of these, 1,003 (82%) women presented with either no reports or incomplete reports of prior HIV testing results at the time of admission to the labor ward. Of 1,222 women, 15 were diagnosed as HIV-positive (on the basis of two rapid tests, dual ELISA and Western blot), yielding a seroprevalence of 1.23% (95% confidence interval [CI] 0.61%–1.8%). Of the 15 HIV test–positive women, four (27%) had presented with reported HIV status, and 11 (73%) new cases of HIV infection were detected due to rapid testing in the labor room. Thus, 11 HIV-positive women received PMTCT interventions on account of round-the-clock rapid HIV testing and counseling in the labor room. While both OraQuick tests (oral and finger-stick) were 100% specific, one false-negative result was documented (with both oral fluid and finger-stick specimens). Of the 15 HIV-infected women who delivered, 13 infants were HIV seronegative at birth and at 1 and 4 mo after delivery; two HIV-positive infants died within a month of delivery.

Conclusions

In a busy rural labor ward setting in India, we demonstrated that it is feasible to introduce a program of round-the-clock rapid HIV testing, including prepartum and extended postpartum counseling sessions. Our data suggest that the availability of round-the-clock rapid HIV testing resulted in successful documentation of HIV serostatus in a large proportion (82%) of rural women who were unaware of their HIV status when admitted to the labor room. In addition, 11 (73%) of a total of 15 HIV-positive women received PMTCT interventions because of round-the-clock rapid testing in the labor ward. These findings are relevant for PMTCT programs in developing countries.

Rapid tests for influenza: Test accuracy

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Diagnostic Accuracy of a Rapid Influenza Test for Pandemic Influenza A H1N1

Aubree Gordon[1,2*], Elsa Videa[3], Saira Saborío[4], Roger López[4], Guillermina Kuan[5], Angel Balmaseda[4], Eva Harris[6]

1 Division of Epidemiology, School of Public Health, University of California, Berkeley, California, United States of America, 2 John E. Fogarty International Center, National Institutes of Health, Bethesda, Maryland, United States of America, 3 Sustainable Sciences Institute, Managua, Nicaragua, 4 Departamento de Virología, Centro Nacional de Diagnóstico y Referencia, Ministry of Health, Managua, Nicaragua, 5 Centro de Salud Sócrates Flores Vivas, Ministry of Health, Managua, Nicaragua, 6 Division of Infectious Diseases and Vaccinology, School of Public Health, University of California, Berkeley, California, United States of America

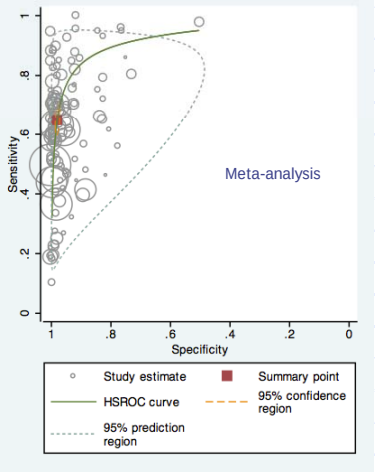
Abstract

Background: With the current influenza A H1N1 pandemic (H1N1pdm), it is extremely important that clinicians can quickly and accurately identify influenza cases.

Methodology/Principal Findings: To investigate the performance of the QuickVue Influenza A+B rapid test, we conducted a prospective study of the diagnostic accuracy of the QuickVue Influenza A+B test compared to real-time reverse transcriptase-polymerase chain reaction (RT-PCR) for influenza A H1N1pdm in Nicaraguan children aged 2 to 14 years. Rapid test sensitivity and specificity compared to real-time RT-PCR were 64.1% (95% CI 53.5, 73.9) and 98.3% (95.0, 99.6), respectively. Agreement between the two tests was 86.4% (95% CI 81.7, 90.3), and kappa was calculated to be 0.67 (95% CI 0.56, 0.76). Performance of the rapid test varied by day of presentation, with a sensitivity of 41.7% (95% CI 22.1, 63.4) for samples from children presenting on the day of symptom onset and a sensitivity of 72.1% (95% CI 59.9, 82.3) for samples from children presenting one or more days post-symptom onset.

Conclusions/Significance: We found that the rapid test performed with moderate sensitivity and high specificity. Test performance varied by day of onset, with lower sensitivity on the day of symptom onset.

Citation: Gordon A, Videa E, Saborío S, López R, Kuan G, et al. (2010) Diagnostic Accuracy of a Rapid Influenza Test for Pandemic Influenza A H1N1. PLoS ONE 5(4): e10364. doi:10.1371/journal.pone.0010364



Chartrand C et al.

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Rapid tests for influenza: Clinical impact

Impact of the Rapid Diagnosis of Influenza on Physician Decision-Making and Patient Management in the Pediatric Emergency Department: Results of a Randomized, Prospective, Controlled Trial

Aleta B. Bonner, DVM, MD*; Kathy W. Monroe, MD*; Lynya I. Talley, PhDS; Ann E. Klasner, MD, MPH*; and David W. Kimberlin, MD‖

ABSTRACT. *Objective.* To determine the impact of the rapid diagnosis of influenza on physician decision-making and patient management, including laboratory tests and radiographs ordered, patient charges associated with these tests, antibiotics/antivirals prescribed, and length of time to patient discharge from the emergency department.

Methods. Patients aged 2 months to 21 years presenting to an urban children's teaching hospital emergency department were screened for fever and cough, coryza, myalgias, headache, and/or malaise. After obtaining informed consent, patients were randomized to 1 of 2 groups: 1) physician receives (physician aware of) the rapid influenza test result; or 2) physician does not receive (physician unaware of) the result. For patients in the physician aware group, nasopharyngeal swabs were obtained, immediately tested with the FluOIA test for influenza A and B, and the result was placed on the chart before patient evaluation by the attending physician. For the physician unaware group, nasopharyngeal swabs were obtained, stored according to manufacturer's directions, and tested within 24 hours. Results for the physician unaware group were not disclosed to the treating physicians at any time. The 2 resultant influenza-positive groups (aware and unaware) were compared for laboratory and radiograph studies and their associated patient charges, antibiotic/antiviral prescriptions, and length of stay in the emergency department.

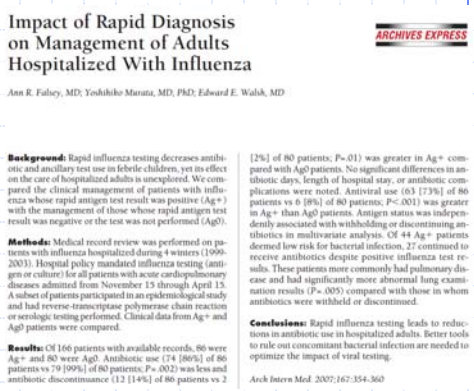
Results. A total of 418 patients were enrolled, and 391 completed the study. Of these, 202 tested positive for influenza. Comparison of the 96 influenza-positive patients whose physician was aware of the result with the 106 influenza-positive patients whose physician was unaware of the result revealed significant reductions among the former group in: 1) numbers of complete blood counts, blood cultures, urinalyses, urine cultures, and chest radiographs performed; 2) charges associated with these tests; 3) antibiotics prescribed; and 4) length of stay in the emergency department. The number of influenza-positive patients who received prescriptions for antiviral drugs was significantly higher among those whose physician was aware of the result.

Conclusions. Physician awareness of a rapid diagnosis of influenza in the pediatric emergency department significantly reduced the number of laboratory tests and radiographs ordered and their associated charges, decreased antibiotic use, increased antiviral use, and decreased length of time to discharge. *Pediatrics* 2003;112:363-367; *pediatric, influenza, physician decision-making, patient management.*

Influenza virus types A and B are common respiratory pathogens in the pediatric population. Depending on age, attack rates may be 1.5 to 3 times higher than for adults, with school-aged children having the highest attack rates.[1,2] A retrospective cohort study of children under 15 years of age demonstrated outpatient visits attributable to influenza ranging from 6 to 15 per 100 children.[3] Infection with influenza virus leads to a significant increase in primary care visits, and also increases in emergency department utilization during wintertime epidemics.[4]

Rapid diagnostic test kits for influenza types A and B are currently available for outpatient use and have proven to be both sensitive and specific.[5–7] Few studies have been performed which analyze the impact of rapid diagnostic testing for influenza and subsequent effect on patient management.[8–11] To date, there are no prospective, randomized studies analyzing use of rapid influenza testing and effect on patient management in the pediatric emergency department. Rapid diagnostic tests are not currently routinely incorporated in the work-up of infants and children with fever and vague symptoms, or with fever and no documented source.[12] Use of rapid tests in the pediatric emergency department which are sensitive and specific for influenza could potentially decrease performance of other more invasive tests, thereby reducing associated patient charges, reducing patient length of stay in the emergency depart-

Pediatrics 2003;112;363-367



Impact of Rapid Diagnosis on Management of Adults Hospitalized With Influenza

ARCHIVES EXPRESS

Ann R. Falsey, MD; Yoshihiko Murata, MD, PhD; Edward E. Walsh, MD

Background: Rapid influenza testing decreases antibiotic and ancillary test use in febrile children, yet its effect on the care of hospitalized adults is unexplored. We compared the clinical management of patients with influenza whose rapid antigen test result was positive (Ag+) with the management of those whose rapid antigen test result was negative or the test was not performed (Ag0).

Methods: Medical record review was performed on patients with influenza hospitalized during 4 winters (1999-2003). Hospital policy mandated influenza testing (antigen or culture) for all patients with acute cardiopulmonary diseases admitted from November 15 through April 15. A subset of patients participated in an epidemiological study and had reverse-transcriptase polymerase chain reaction or serologic testing performed. Clinical data from Ag+ and Ag0 patients were compared.

Results: Of 166 patients with available records, 86 were Ag+ and 80 were Ag0. Antibiotic use (74 [86%] of 86 patients vs 79 [99%] of 80 patients; $P = .002$) was less and antibiotic discontinuance (12 [14%] of 86 patients vs 2 [2%] of 80 patients; $P = .01$) was greater in Ag+ compared with Ag0 patients. No significant differences in antibiotic days, length of hospital stay, or antibiotic complications were noted. Antiviral use (63 [73%] of 86 patients vs 0 [0%] of 80 patients; $P < .001$) was greater in Ag+ than Ag0 patients. Antigen status was independently associated with withholding or discontinuing antibiotics in multivariate analysis. Of 44 Ag+ patients deemed low risk for bacterial infection, 27 continued to receive antibiotics despite positive influenza test results. These patients more commonly had pulmonary disease and had significantly more abnormal lung examination results ($P = .005$) compared with those in whom antibiotics were withheld or discontinued.

Conclusions: Rapid influenza testing leads to reductions in antibiotic use in hospitalized adults. Better tools to rule out concomitant bacterial infection are needed to optimize the impact of viral testing.

Arch Intern Med. 2007;167:354-360

"Impact" outcomes include:

- Change in clinical decisions
- Reduction in antibiotic use
- Increased antiviral use
- Decreased length of time to discharge
- Reduction in lab investigations, etc

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Most diagnostic studies are focused on technical and accuracy issues

Table 1. **Hierarchy of Diagnostic Evaluation and the Number of Studies Available for Different Levels of Diagnostic Test in a Technology Assessment of Magnetic Resonance Spectroscopy for Brain Tumors***

Level	Description	Examples of Study Purpose or Measures	Studies Available, *n*	Patients, *n*
1	Technical feasibility and optimization	Ability to produce consistent spectra	85	2434
2	Diagnostic accuracy	Sensitivity and specificity	8	461
3	Diagnostic thinking impact	Percentage of times clinicians' subjective assessment of diagnostic probabilities changed after the test	2	32
4	Therapeutic choice impact	Percentage of times therapy planned before MRS changed after the test	2	105
5	Patient outcome impact	Percentage of patients who improved with MRS diagnosis compared with those without MRS (e.g., survival, quality of life)	0	0
6	Societal impact	Cost-effectiveness analysis (e.g., use to detect tumor in asymptomatic population)	0	0

* MRS = magnetic resonance spectroscopy.

Tatsioni, Annals

ANALYSIS

RATING QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

GRADE: grading quality of evidence and strength of recommendations for diagnostic tests and strategies

The GRADE system can be used to grade the quality of evidence and strength of recommendations for diagnostic tests or strategies. This article explains how patient-important outcomes are taken into account in this process

SUMMARY POINTS

As for other interventions, the GRADE approach to grading the quality of evidence and strength of recommendations for diagnostic tests or strategies provides a comprehensive and transparent approach for developing recommendations

Cross sectional or cohort studies can provide high quality evidence of test accuracy

However, test accuracy is a surrogate for patient-important outcomes, so such studies often provide low quality evidence for recommendations about diagnostic tests, even when the studies do not have serious limitations

Inferring from data on accuracy that a diagnostic test or strategy improves patient-important outcomes will require the availability of effective treatment, reduction of test related adverse effects or anxiety, or improvement of patients' wellbeing from prognostic information

Judgments are thus needed to assess the directness of test results in relation to consequences of diagnostic recommendations that are important to patients

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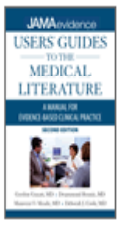

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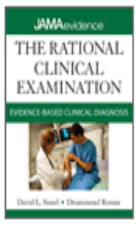

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