Diagnostic Studies

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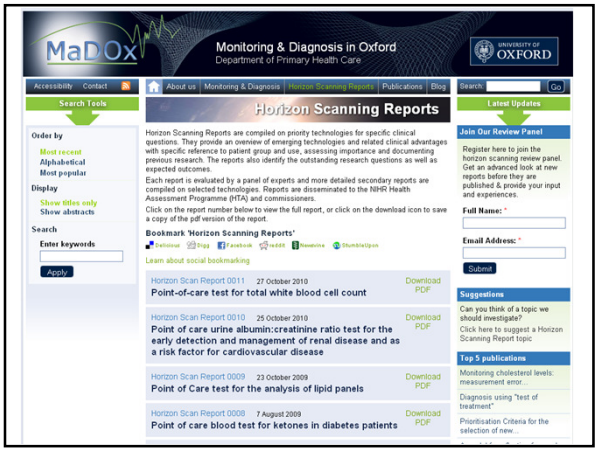
www.madox.org



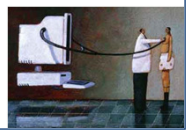
Diagnostic tests: What you need to know

- Validity of a diagnostic study
- Interpret the results

"Mr. Osborne, may I be excused! My brain is full."

What is diagnosis?

The process of identifying a disease by its signs, symptoms and results of various diagnostic procedures



Diagnosis

Typically someone with abnormal ***symptoms*** consults a physician, who will obtain a history of their illness and examine them for ***signs*** of diseases.

The physician formulates a hypothesis of likely diagnoses and may or may not order further ***tests*** to clarify the diagnosis

Diagnosis has different meanings in different contexts

Pathologist: identification of disease in terms of histological or chemical changes

Bacteriologist: identification of disease in terms of the infective agent

Diagnosis has different meanings in different contexts

Specialist doctor:

The focal point of thought in the treatment of a patient.

Diagnosis, gives a name to the patient's ailment, the thinking goes backward to decide about pathogenesis, and forward to predict prognosis and choose therapy.

Feinstein A. 1967

Diagnosis has different meanings in different contexts

Family doctor:

Diagnosis is an assessment of his patient's physical, psychological and social condition.

What are tests used for?

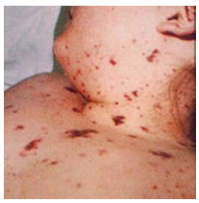
- Increase certainty about presence/absence of disease
- Disease severity
- Monitor clinical course
- Assess prognosis – risk/stage within diagnosis
- Plan treatment e.g., location
- Stall for time!

Diagnostic stages & strategies

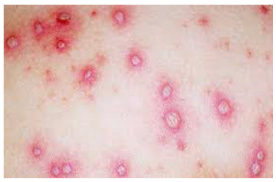
Stage	Strategies used
Initiation of the diagnosis	•Spot diagnoses •Self-labelling •Presenting complaint •Pattern recognition
Refinement of the diagnostic causes	•Restricted Rule Outs •Stepwise refinement •Probabilistic reasoning •Pattern recognition fit •Clinical Prediction Rule
Defining the final diagnosis	•Known Diagnosis •Further tests ordered •Test of treatment •Test of time •No label

(Heneghan et al, BMJ 2009)

Not all diagnosis need tests?



Meningitis

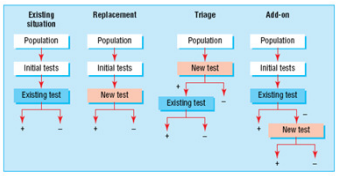


Chicken Pox

Roles of new tests

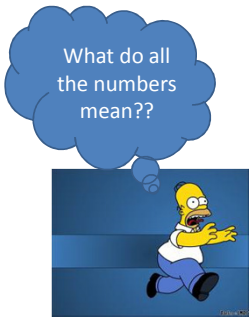
- **Replacement** – new replaces old
  - E.g. CT colonography for barium enema
- **Triage** – new determines need for old
  - E.g. B-natriuretic peptide for echocardiography
- **Add-on** – new combined with old
  - E.g. ECG and myocardial perfusion scan

Bossuyt et al BMJ 2006;332:1089–92



Roles of tests and positions in existing diagnostic pathways

Interpreting Diagnostic Studies



Diagnostic Studies

Series of patients

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Index test

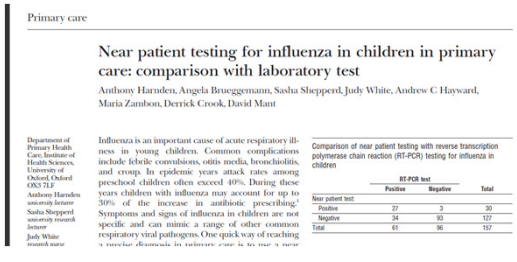
↓

Reference ("gold") standard

↓

Compare the results of the index test with the reference standard, blinded

Diagnostic Study Example



Primary care

Near patient testing for influenza in children in primary care: comparison with laboratory test

Anthony Harnden, Angela Brueggemann, Sasha Shepperd, Judy White, Andrew C Hayward, Maria Zambon, Derrick Crook, David Mant

Department of Primary Health Care, Institute of Health Sciences, University of Oxford, Oxford OX3 7LF
Anthony Harnden university lecturer
Sasha Shepperd university research lecturer
Judy White research nurse

Influenza is an important cause of acute respiratory illness in young children. Common complications include febrile convulsions, otitis media, bronchiolitis, and croup. In epidemic years attack rates among preschool children often exceed 40%. During these years children with influenza may account for up to 30% of the increase in antibiotic prescribing.[1] Symptoms and signs of influenza in children are not specific and can mimic a range of other common respiratory viral pathogens. One quick way of reaching

Comparison of near patient testing with reverse transcription polymerase chain reaction (RT-PCR) testing for influenza in children

	RT-PCR test		
Near patient test:	Positive	Negative	Total
Positive	27	3	30
Negative	34	93	127
Total	61	96	157

Appraising diagnostic tests: 3 easy steps

Are the results valid?

- Appropriate spectrum of patients?
- Does everyone get the gold standard?
- Is there an independent, blind or objective comparison with the gold standard?

↓

What are the results?

↓

Will they help me look after my patients?

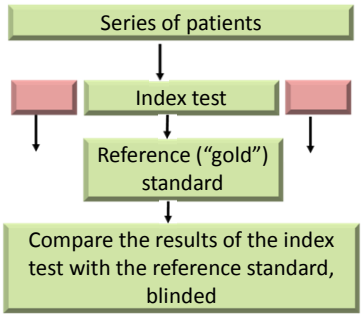
1. *Appropriate spectrum* of patients?

- Ideally, test should be performed on a group of patients in whom it will be applied in the real world clinical setting
- **Spectrum bias** = study using only highly selected patients…….perhaps those in whom you would really suspect have the diagnosis

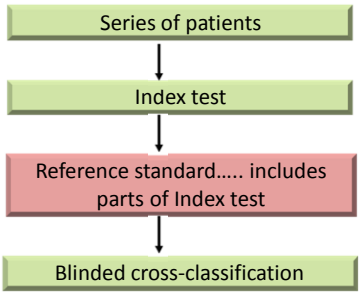
2. Do all patients have the *gold standard*?

- Ideally all patients get the gold /reference standard test
- **Work-up bias** = only **some** patients get the gold standard…..probably the ones in whom you really suspect have the disease

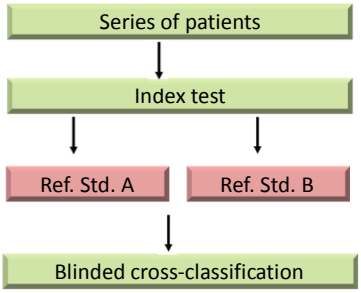
Verification (work-up) Bias



Incorporation Bias



Differential Reference Bias



3. *Independent, blind or objective comparison* with the gold standard?

- Ideally, the gold standard is independent, blind and objective
- **Observer bias** = test is very subjective, or done by person who knows something about the patient

Observer Bias

Series of patients

↓

Index test

↓

Reference ("gold") standard

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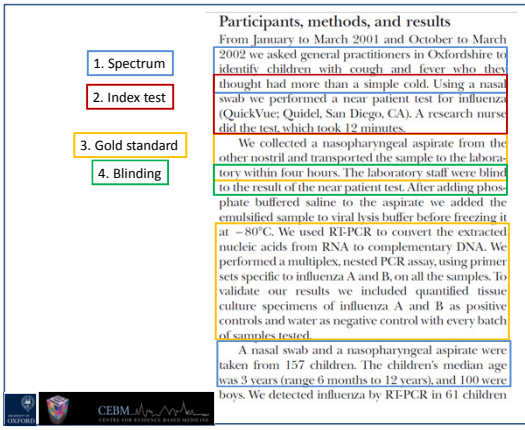
Unblinded cross-classification



1. Spectrum
2. Index test
3. Gold standard
4. Blinding

Participants, methods, and results

From January to March 2001 and October to March 2002 we asked general practitioners in Oxfordshire to identify children with cough and fever who they thought had more than a simple cold. Using a nasal swab we performed a near patient test for influenza (QuickVue; Quidel, San Diego, CA). A research nurse did the test, which took 12 minutes.

We collected a nasopharyngeal aspirate from the other nostril and transported the sample to the laboratory within four hours. The laboratory staff were blind to the result of the near patient test. After adding phosphate buffered saline to the aspirate we added the emulsified sample to viral lysis buffer before freezing it at −80°C. We used RT-PCR to convert the extracted nucleic acids from RNA to complementary DNA. We performed a multiplex, nested PCR assay, using primer sets specific to influenza A and B, on all the samples. To validate our results we included quantified tissue culture specimens of influenza A and B as positive controls and water as negative control with every batch of samples tested.

A nasal swab and a nasopharyngeal aspirate were taken from 157 children. The children's median age was 3 years (range 6 months to 12 years), and 100 were boys. We detected influenza by RT-PCR in 61 children

Appraising diagnostic tests

Are the results valid?

- Appropriate spectrum of patients?
- Does everyone get the gold standard?
- Is there an independent, blind or objective comparison with the gold standard?

↓

What are the results?

- Sensitivity, specificity
- Likelihood ratios
- Positive and Negative Predictive Values

↓

Will they help me look after my patients?

A nasal swab and a nasopharyngeal aspirate were taken from 157 children. The children's median age was 3 years (range 6 months to 12 years), and 100 were boys. We detected influenza by RT-PCR in 61 children (39%). The near patient test was positive in 27 of these 61 children, giving a sensitivity of 44% (95% confidence interval 32% to 58%) and a specificity of 97% (91% to 99%) (table). The likelihood ratio for a positive test result was 14.2 (4.5 to 44.7) and for a negative result 0.58 (0.46 to 0.72).

The 2 by 2 table

Test \ Disease	+	−
+	True positives	False positives
−	False negatives	True negatives

The 2 by 2 table: Sensitivity

Test \ Disease	+	−
+	84 a True positives	
−	16 c False negatives	

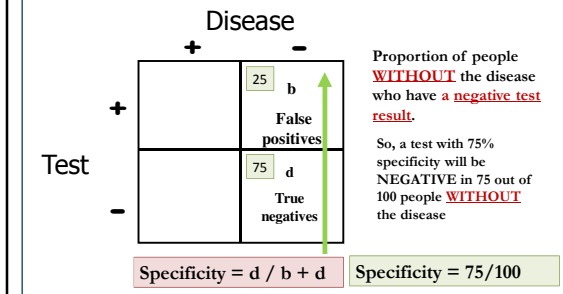
Proportion of people WITH the disease who have a positive test result.

So, a test with 84% sensitivity….means that the test identifies 84 out of 100 people WITH the disease

Sensitivity = a / a + c

Sensitivity = 84/100

The 2 by 2 table: Specificity



Proportion of people WITHOUT the disease who have a negative test result.

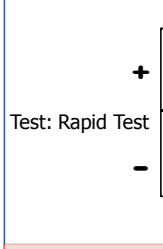
So, a test with 75% specificity will be NEGATIVE in 75 out of 100 people WITHOUT the disease

Specificity = d / b + d

Specificity = 75/100

The Influenza Example

Disease: Lab Test



There were 61 children who had influenza…the rapid test was positive in 27 of them

There were 96 children who did not have influenza… the rapid test was negative in 93 of them

Sensitivity = 27/61 = 0.44 (44%)

Specificity = 93/96 = 0.97 (97%)

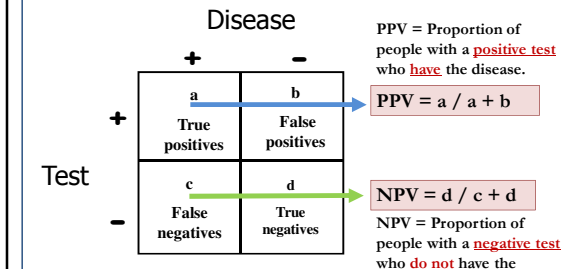
A nasal swab and a nasopharyngeal aspirate were taken from 157 children. The children's median age was 3 years (range 6 months to 12 years), and 100 were boys. We detected influenza by RT-PCR in 61 children (39%). The near patient test was positive in 27 of these 61 children, giving a sensitivity of 44% (95% confidence interval 32% to 58%) and a specificity of 97% (91% to 99%) (table). The likelihood ratio for a positive test result was 14.2 (4.5 to 44.7) and for a negative result 0.58 (0.46 to 0.72).

Tip

- **Sensitivity** is useful to me
  - 'The new rapid influenza test was positive in 27 out of 61 children with influenza (sensitivity = 44%)'
- Specificity seems a bit confusing!
  - 'The new rapid influenza test was negative in 93 of the 96 children who did not have influenza (specificity = 97%)'
- So…the **false positive rate** is sometimes easier

  False positive rate = 1 - specificity
  - 'There were 96 children who did not have influenza… the rapid test was falsely positive in 3 of them'
  - So a specificity of 97% means that the new rapid test is wrong (or falsely positive) in 3% of children

Positive and Negative Predictive Value



PPV = Proportion of people with a positive test who have the disease.

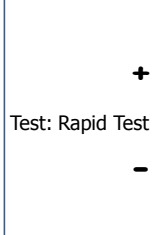
PPV = a / a + b

NPV = d / c + d

NPV = Proportion of people with a negative test who do not have the disease.

The Influenza Example

Disease: Lab Test



PPV = 27/30 = 90%

NPV = 93/127 = 73%

Positive and Negative Predictive Value

NOTE

•PPV and NPV are not intrinsic to the test – they also depend on the prevalence!

•NPV and PPV should only be used **if the ratio of the number of patients in the disease group and the number of patients in the healthy control group is equivalent to the prevalence** of the diseases in the studied population

•Use Likelihood Ratio - does not depend on prevalence

Likelihood ratios

Positive likelihood ratio (LR+)

How much more likely is a positive test to be found in a person with the disease than in a person without it?

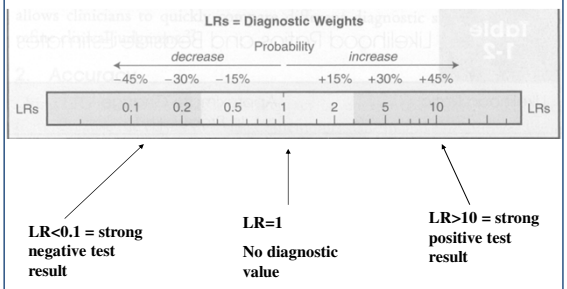
LR+ = sens/(1-spec)

Negative likelihood ratio (LR-)

How much more likely is a negative test to be found in a person without the condition than in a person with it?

LR- = (1-sens)/(spec)

What do likelihood ratios mean?



LR<0.1 = strong negative test result

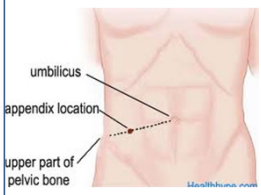
LR=1

No diagnostic value

LR>10 = strong positive test result

Diagnosis of Appendicitis

McBurney's point



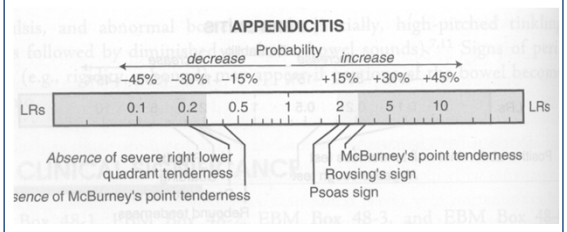
Rovsing's sign

If palpation of the left lower quadrant of a person's abdomen results in more pain in the right lower quadrant

Psoas sign

Abdominal pain resulting from passively extending the thigh of a patient or asking the patient to actively flex his thigh at the hip

For Example



McGee: Evidence based Physical Diagnosis (Saunders Elsevier)

Appraising diagnostic tests

Are the results valid?

- Appropriate spectrum of patients?
- Does everyone get the gold standard?
- Is there an independent, blind or objective comparison with the gold standard?

What are the results?

- Sensitivity, specificity
- Likelihood ratios
- Positive and Negative Predictive Values

Will they help me look after my patients?

- Can I do the test in my setting?
- Do results apply to the mix of patients I see?
- Will the result change my management?
- Costs to patient/health service?

Will the test apply in my setting?

- Reproducibility of the test and interpretation in my setting
- Do results apply to the mix of patients I see?
- Will the results change my management?
- Impact on outcomes that are important to patients?
- Where does the test fit into the diagnostic strategy?
- Costs to patient/health service?

Reliability – how reproducible is the test?

- Kappa = measure of inter-observer reliability

Value of Kappa	Strength of Agreement
<0.20	Poor
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Good
0.81-1.00	Very Good

Test	Kappa value
Tachypnoea	0.25
Crackles on auscultation	0.41
Pleural rub	0.52
Chest XRay for cardiomegaly	0.48
MRI spine for disc herniation	0.59

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10 August 2010 Last updated at 22:01

New brain scan to diagnose autism

By Jane Hughes
Health correspondent, BBC News

A brain scan that detects autism in adults could mean much more straightforward diagnosis of the condition, scientists say.

Experts at King's College London said the scan - tested on 40 people - identified tiny but crucial signs of autism, only detectable by computer.

Current methods of diagnosis can be lengthy and expensive.

But some experts say further research will be needed before the new technique can be widely used.

The computer scan shows up a distinctive pattern associated with autism

The researchers detected autism with over 90% accuracy, the Journal of Neuroscience reports.

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Why autism can't be diagnosed with brain scans

Using brain scans to detect autism would be a huge expensive waste of money, says Carl Heneghan

The BBC, the Guardian and Reuters this week widely reported British researchers published in the Journal of Neuroscience have developed a brain scan which can detect autism in adults with 90% accuracy.

Dr Christine Ecker, the lead author, showed her imaging technique was able to detect which people in her group had autism. "If we get a new case, we will also hopefully be 90% accurate," she said.

Pretty simple then, you turn up, have the test, and you have a 90% chance of finding out whether you have autism.

Well, you couldn't be any further from the truth.

(108) | Tweet | 170 | Comments (47)

Posted by Carl Heneghan Thursday 12 August 2010 15.29 BST
guardian.co.uk

A larger | smaller

Science
Medical research

Natural Frequencies

Your friend, the avid Guardian Reader, reads Carl's commentary and asks you:

"Well, you're the Doctor, what's going on here? Who is right? If my child had this test and it was positive, what's the chance my child has autism?? "

Neurobiology of Disease

Describing the Brain in Autism in Five Dimensions—Magnetic Resonance Imaging-Assisted Diagnosis of Autism Spectrum Disorder Using a Multiparameter Classification Approach

Christine Ecker,[1] Andre Marquand,[2,3] Janaina Mourão-Miranda,[3,4] Patrick Johnston,[5] Eileen M. Daly,[1] Michael J. Brammer,[3] Stefanos Maltezos,[1] Clodagh M. Murphy,[1] Dene Robertson,[1] Steven C. Williams,[3] and Declan G. M. Murphy[1]
[1]Section of Brain Maturation, Department of Psychological Medicine, Institute of Psychiatry, [2]Brain Image Analysis Unit, Department of Biostatistics, Institute of Psychiatry, and [3]Centre for Neuroimaging Sciences, Institute of Psychiatry, King's College, London SE5 8AF, United Kingdom, and [4]Centre for Computational Statistics and Machine Learning, Department of Computer Science, University College London, London WC1E 6BT, United Kingdom

The National Autistic Society

Estimated prevalence rate in the UK

The indication from recent studies is that the figures cannot be precisely fixed, but it appears that a prevalence rate of around 1 in 100 is a best estimate of the prevalence in children. No prevalence studies have ever been carried out on adults.

Table 3. Results of SVM classification between ASD and control group using different brain morphometric features in the left and right hemispheres

Morphometric feature	Correctly classified (%)	Sensitivity (%)	Specificity (%)	p
Left hemisphere				
All parameters	85	90	80	0*
Cortical thickness	90	90	90	0*
Radial curvature	72.5	65	80	<0.001
Average convexity	70	75	65	<0.004
Metric distortion	80	80	80	0*
Pial area	77.5	70	85	0*
Right hemisphere				
All parameters	65	60	70	<0.03
Cortical thickness	60	65	55	<0.01
Radial curvature	52.5	50	55	<0.30
Average convexity	50	40	60	<0.40
Metric distortion	57.5	45	70	<0.06
Pial area	45	45	45	<0.60

Correctly identified ASD cases were considered true positive. *p values of zero indicate that not a single one of the 1000 permutations provided a better classification.

Natural Frequencies

Autism has a prevalence of 1%.

The test has sensitivity of 90% and specificity of 80%.

- 100% — Always
- 50% — Maybe
- 0% — Never

Natural Frequencies

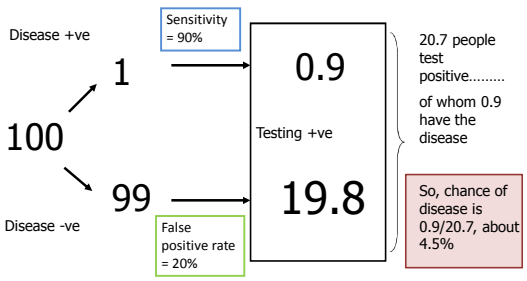
Autism has a prevalence of 1%.

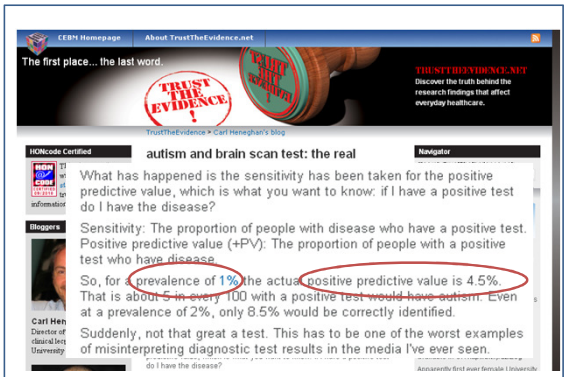
The test has sensitivity of 90% and specificity of 80%.

If the test is positive, what are the chances he/she has the disease?

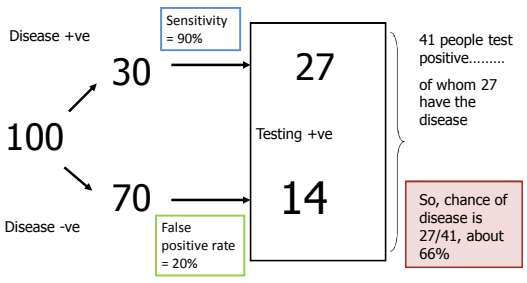
End

Prevalence of 1%, Sensitivity of 90%, Specificity of 80%





Prevalence of 30%, Sensitivity of 90%, Specificity of 80%



What is the ONE thing I need to remember from today?

Are the results valid?

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What are the results?

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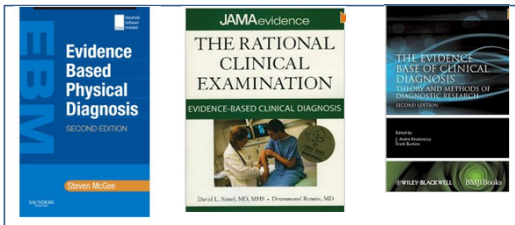
Will they help me look after my patients?

Don't believe everything you are told, Ask for the Evidence!



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Comparative accuracy: assessing new tests against existing diagnostic pathways.
Bossuyt PM, Irwig L, Craig J, Glasziou P. BMJ. 2006 May 6;332(7549):1089-92.

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