

# Diagnostic Studies

*Dr. Annette Plüddemann*

*Nuffield Department of Primary Care Health Sciences  
Centre for Evidence-Based Medicine*





# MSc in Evidence-Based Health Care

The MSc in Evidence-Based Health Care will position students to integrate the best available research evidence with their clinical expertise and patient values to make better informed decisions in their field of health care.



This is a joint programme between the Nuffield Department of Primary Care Health Sciences and the Department for Continuing Education's Continuing Professional Development Centre. The Programme works in collaboration with the renowned Centre for Evidence-Based Medicine in Oxford.

This programme has teachers and contributors who are internationally recognised leaders in the field of evidence-based practice and teaching. The flexible structure of the course has been devised to fit with the structure of specialist training and to accommodate student choice.

**Watch the following video for more information about the Programme and the student experience:**



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### Key facts

Part-time: 2-4 years

Start Date: October 2017

Course status: Open

Application deadlines are noon (GMT) 20 January 2017 & 10 March 2017

#### Fee rates for the academic year 2017/18

Annual Award Fee: £5,910

Module fee: each £1,795 (per taught module, 6 required)

# Evidence-Based Diagnosis and Screening



## Overview

*Evaluating and interpreting the evidence for diagnostic tests*

This module will teach students how to critically appraise and apply the best evidence on diagnostic tests. They will learn how to evaluate and interpret the diagnostic accuracy of tests and procedures in different settings. They will also learn how the evidence can inform screening and monitoring programmes.

The last date for receipt of complete applications is 5pm Friday 6th January 2017. Regrettably, late applications cannot be accepted.

The overall aims of this module are to enable students to:

- Understand the different purposes for doing tests, and the appropriate means to evaluate tests for those purposes
- Be able to formulate focused questions for different diagnostic problems
- Be able to describe the optimal study design to carry out clinical research for the investigation of those questions
- Be able to search effectively for papers for different types of diagnostic questions
- Be able to appraise diagnostic accuracy studies
- Have an understanding of reporting standards for diagnostic test studies
- Know how to appraise systematic reviews of diagnostic studies
- Be able to describe different forms of design-related biases in diagnostic studies
- Be able to understand and calculate various measures of diagnostic accuracy, including sensitivity and specificity and positive and negative likelihood ratio
- Understand how information from multiple diagnostic tests can be evaluated simultaneously
- Understand and be able to determine a basic sample size calculation for a simple diagnostic study
- Have an understanding of how to present results of diagnostic test studies visually and graphically
- Understand how results of research studies influence clinical decisions
- Understand how results of diagnostic tests should be communicated to clinicians
- Have an understanding of the adoption of diagnostic test services into clinical practice
- Understand the pitfalls and problems of screening programmes
- Understand the interplay of diagnosis and monitoring in clinical practice



## Course summary

- Mon 23 Jan 2017 to Fri 27 Jan 2017
- Rewley House, 1 Wellington Square, Oxford, Oxfordshire, OX1 2JA.
- From £1740.00
- 20 CATS points
- Course code O16C182B9J
- cpdhealth@conted.ox.ac.uk
- +44 (0) 1865 286943
- Applications not yet being accepted

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## Terms and conditions

For applicants and students on this course

### Sources of funding

Find information on the different ways in which we may be able to help to support you financially whilst you are studying with us.



# Horizon scanning reports

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The horizon scanning reports summarise why the technology is important, provide an overview of the current available evidence and assess whether it could be adopted in the NHS and if so, what the requirements are for the delivery of the technology into practice.

These reports are freely accessible and disseminated to the NIHR Health Technology Assessment Programme (HTA), the National Institute for Health and Clinical Excellence (NICE) and commissioners of health care services to facilitate adoption and identify further research requirements.

We are funded by the National Institute for Health Research (NIHR) and collaborate with the Health Economics Research Centre at Oxford University.

[Find out more about our research](#)



The Oxford Diagnostic Horizon Scan Programme identifies new and emerging diagnostic technologies relevant to primary care in the NHS.

46. Point-of-care devices for detecting diabetic polyneuropathy

[Read](#) | [Download PDF](#)

45. Point-of-care testing for urinary tract infections

[Read](#) | [Download PDF](#)

44. Point-of-care HbA1c tests: diagnosis of diabetes

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BMJ Quality & Safety Online First, published on 7 July 2012 as 10.1136/bmjqs-2012-001159

Original research

## Preventable deaths due to problems in care in English acute hospitals: a retrospective case record review study

Helen Hogan,<sup>1</sup> Frances Healey,<sup>2</sup> Graham Neale,<sup>3</sup> Richard Thomson,<sup>4</sup> Charles Vincent,<sup>3</sup> Nick Black<sup>1</sup>

**ABSTRACT**  
**Introduction:** Monitoring hospital mortality rates is widely recommended. However, the number of preventable deaths remains uncertain with estimates in England ranging from 840 to 40 000 per year, these being derived from studies that identified adverse events but not whether events contributed to death or shortened life expectancy of those affected.  
**Methods:** Retrospective case record reviews of 1000 adults who died in 2009 in 10 acute hospitals in England were undertaken. Trained physician reviewers examined life expectancy and identified

255 000 NHS patients each year suffer serious disability or death as a result of healthcare interventions.<sup>2</sup> This estimate was derived from retrospective case record review (RCRR) studies conducted in USA in the 1980s and 90s.<sup>3-4</sup> These and other national studies using comparable methods were not designed to establish the proportion of deaths that were preventable.<sup>5-8</sup> Two smaller studies have specifically assessed the degree to which problems in

- clinical monitoring (such as failure to act upon test results or monitor patients appropriately) – identified as a problem in 31% of preventable deaths
- diagnosis (such as problems with physical examination or failure to seek a specialist opinion) – identified as a problem in 30% of preventable deaths
- drugs or fluid management – identified as a problem in 21% of preventable deaths

<sup>1</sup>Department of Health Services Research & Policy, London School of Hygiene & Tropical Medicine, London, UK  
<sup>2</sup>National Patient Safety Agency, London, UK  
<sup>3</sup>Clinical Safety Research Unit, Imperial College, London, UK  
<sup>4</sup>Institute of Health and Society, University of Newcastle, Newcastle upon Tyne, UK



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17 January 2013 Last updated at 12:19

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## Phone apps may delay skin cancer diagnosis

Using a smartphone app to decide whether a mole is cancerous could delay sometimes life-saving treatment, according to American researchers.

The University of Pittsburgh scientists put four applications to the test by showing them 100 pictures of cancers and less concerning skin conditions.

Three of the apps wrongly labeled the cancerous lesions as unproblematic in almost a third of cases.

Doctors warn using phones rather than seeking expert help could be harmful.

The research, published in the journal JAMA Dermatology, looked at four commonly used applications.

The images selected to test the apps were all of skin lesions that were later removed and checked for an accurate diagnosis.

Three of the apps analysed the pictures using automated algorithms, without the involvement of doctors.

But users submitting pictures to the fourth app had their images reviewed by a qualified skin specialist.

In this case only one out of 53 cancerous lesions was misdiagnosed, but this app cost \$5 (£3.10) per use.

Dr Paul Ferris, lead researcher of the study, said: "It is important that



Researchers say you must seek medical advice if you are concerned about a mole

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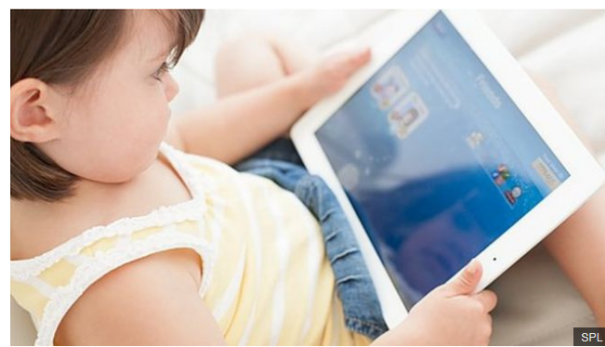
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## Tablet and phone games could help diagnose autism, study suggests

30 August 2016 | Glasgow & West Scotland

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Autism could be diagnosed by allowing children to play games on smart phones and tablets, according to a study.

Researchers from the University of Strathclyde used games on a tablet to track the player's hand movements.

The information gathered helped them to identify those children who may have autism.

The study outlines how technology could offer an accessible and less intrusive way to diagnose the developmental disorder.

Anzulewicz A, Sobota K, Delafield-Butt JT. Toward the Autism Motor Signature: Gesture patterns during smart tablet gameplay identify children with autism. Sci Rep. 2016 Aug 24;6:31107.

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Former England boss Sam Allardyce has not ruled out a return to football after leaving his job with the national side in disgrace.  
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BMJ

BMJ 2013;347:f5125 doi: 10.1136/bmj.f5125 (Published 9 September 2013)

# ANALYSIS

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Health Ho

## The fa annou clinics t 18 month

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- Rate of successfu

By TIM SHIPMAN

PUBLISHED: 22:48, 4 November 2012

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### TOO MUCH MEDICINE

## Political drive to screen for pre-dementia: not evidence based and ignores the harms of diagnosis

David G Le Couteur professor of geriatric medicine<sup>1</sup>, Jenny Doust professor of clinical epidemiology<sup>2</sup>, Helen Creasey dementia specialist<sup>3</sup>, Carol Brayne professor of public health<sup>4</sup>

<sup>1</sup>Centre for Education and Research on Ageing, ANZAC Medical Research Institute and the Charles Perkins Centre, University of Sydney and Sydney Research, Concord, 2139, Australia; <sup>2</sup>Centre for Research in Evidence Based Practice, Bond University, Robina, Australia; <sup>3</sup>Centre for Education and Research on Ageing, Concord RG Hospital; <sup>4</sup>Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

Current policy in many countries is aimed at increasing the rates of diagnosis of dementia and cognitive impairment.<sup>1-3</sup> This policy drive has been accompanied by research into early detection of dementia, including preclinical identification of underlying neurobiology that might later be associated with dementia.<sup>4</sup>

evidence to support their use.<sup>15</sup> Little attention has been paid to the fact that attending memory clinics generates stress for patients<sup>16</sup> and their carers,<sup>17</sup> and expands the use of biomarker testing (cerebrospinal fluid measurements of amyloid and tau) and neuroimaging,<sup>18, 19</sup> with associated costs and morbidity.

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# What is diagnosis?

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

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.

## **Family doctor:**

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

Feinstein A. 1967



# Diagnostic strategies and what tests are used for



# How do clinicians make diagnoses?

- Patient history...examination...differential diagnosis...final diagnosis



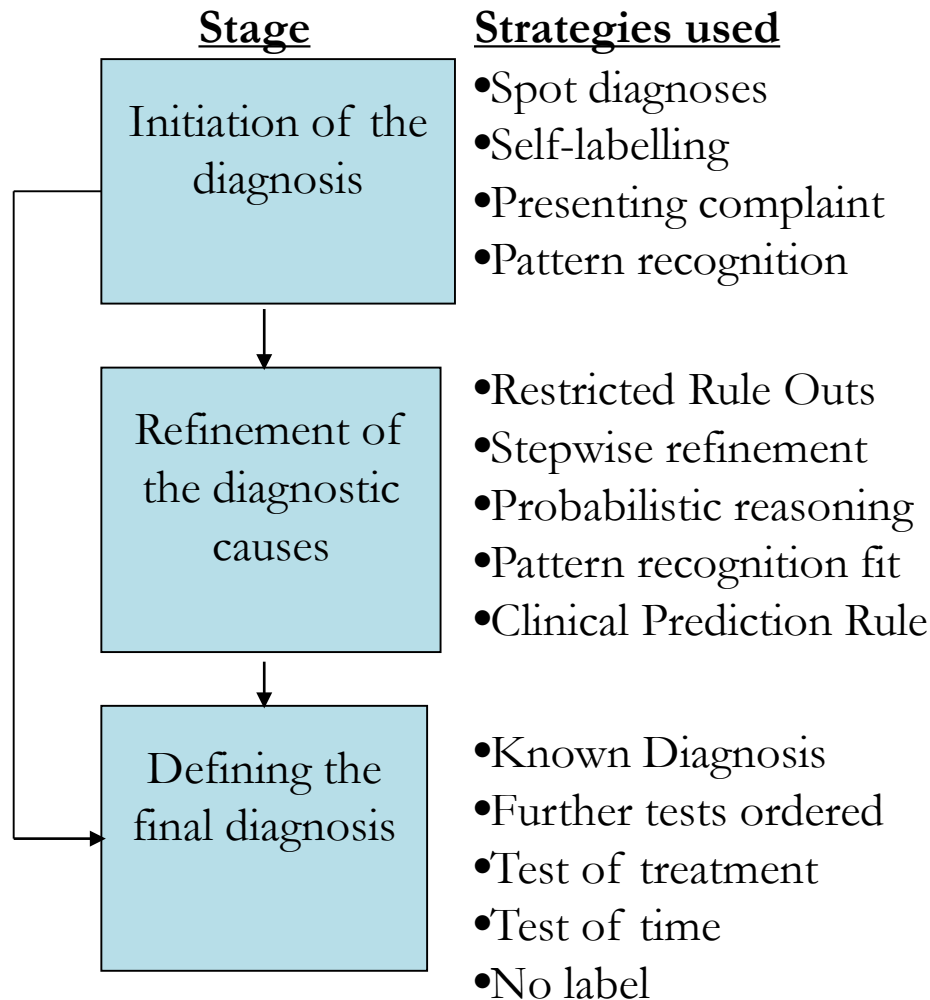
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# Diagnostic stages & strategies

- Aim: identify types and frequency of diagnostic strategies used in primary care
  - 6 GPs collected and recorded strategies used on 300 patients.

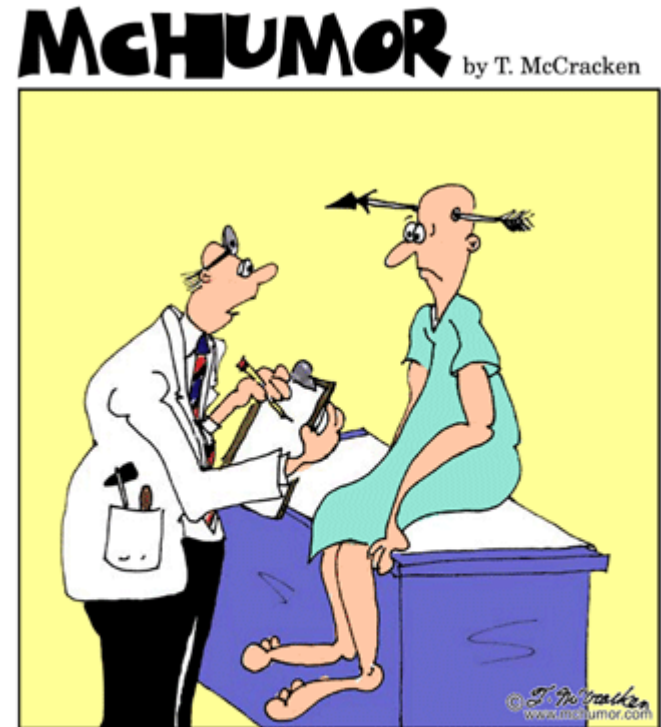


(Diagnostic strategies used in primary care. Heneghan, et al., *BMJ* 2009. 20;338:b9462009)



# 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!



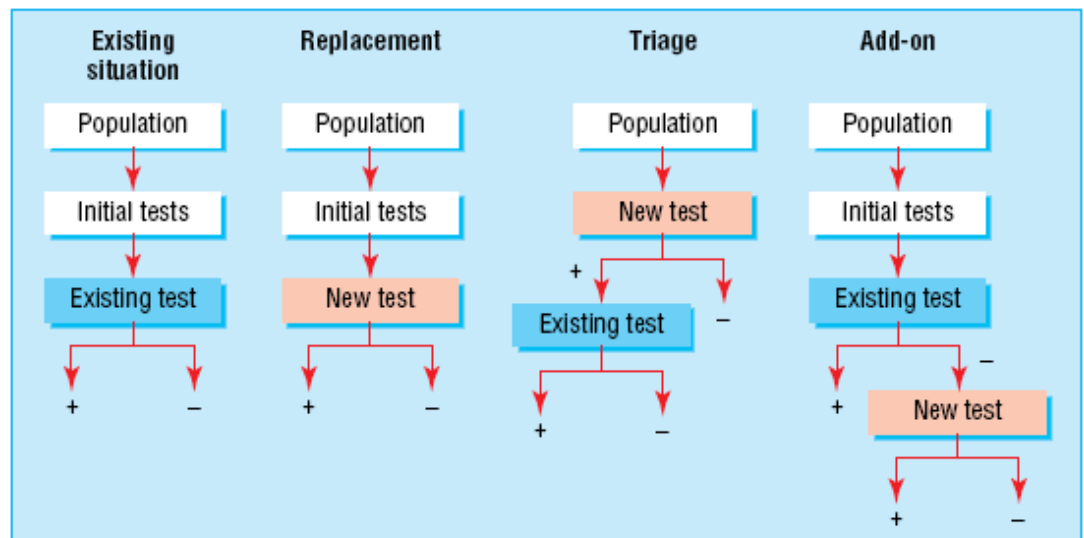
"Off hand, I'd say you're suffering from an arrow through your head, but just to play it safe, I'm ordering a bunch of tests."





# 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

# Critical appraisal of a diagnostic accuracy study



# 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."



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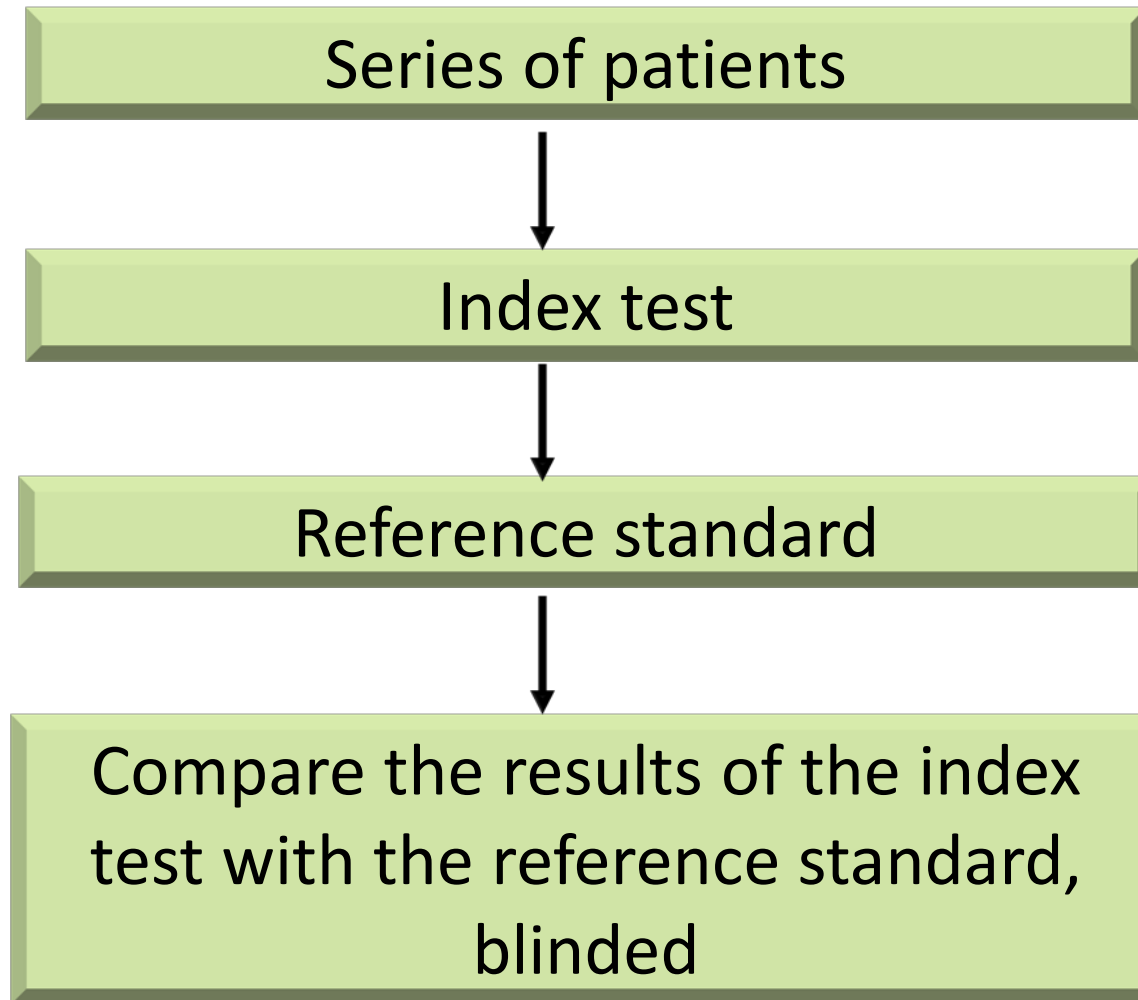
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# Defining the clinical question: PICO or PIRT

- Patient/Problem  
How would I describe a group of patients similar to mine?
- Index test  
Which test am I considering?
- Comparator... or ...Reference Standard  
What is the best reference standard to diagnose the target condition?
- Outcome....or....Target condition  
Which condition do I want to rule in or rule out?



# Diagnostic Accuracy Studies





# 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.<sup>1</sup> 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 a precise diagnosis in primary care is to use a near

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

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



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# Appraising diagnostic studies: 3 easy steps

Are the results valid?

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

What are the results?

Will they help me look after my patients?



# Biases in Diagnostic Accuracy Studies...

## The Ugly 5....



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# 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 uses only highly selected patients.....perhaps those in whom you would really suspect have the diagnosis



# Case-control vs consecutive



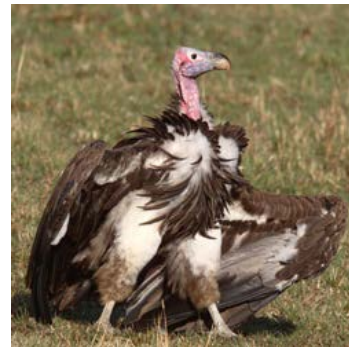


## 2. Do all patients have the *reference standard*?

Ideally all patients get the reference standard test

### **Verification bias:**

only **some** patients get the reference standard.....probably the ones in whom you really suspect have the disease





# Partial Reference Bias

Series of patients



Index test



Ref. Std. A

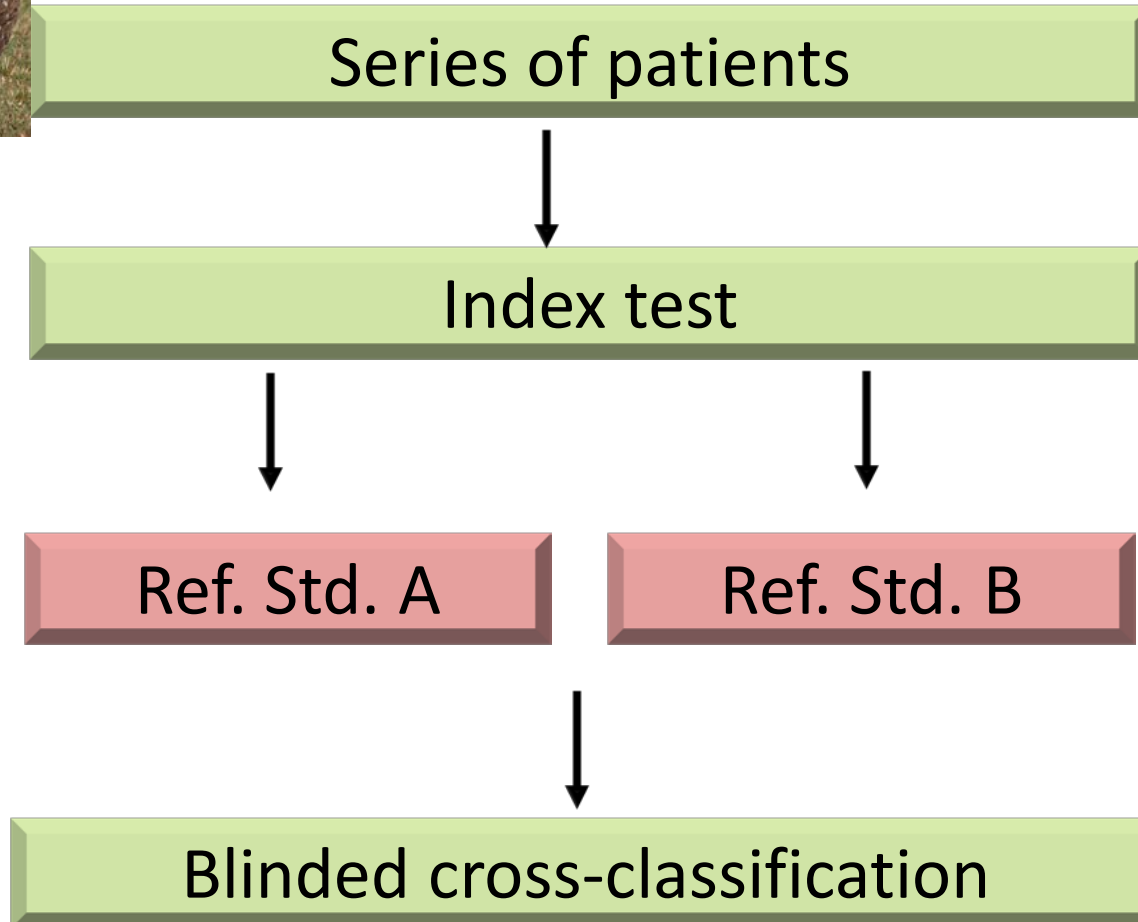


Compare the results of the index test with the reference standard, blinded





# Differential Reference Bias





# Incorporation Bias

Series of patients



Index test



Reference standard.... includes  
parts of Index test

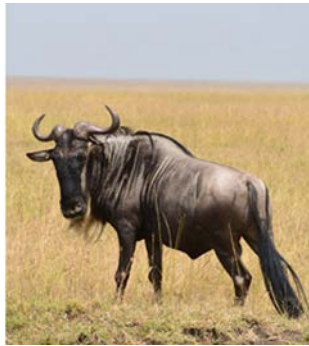


Blinded cross-classification



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

Ideally, the reference standard is independent,  
blind and objective

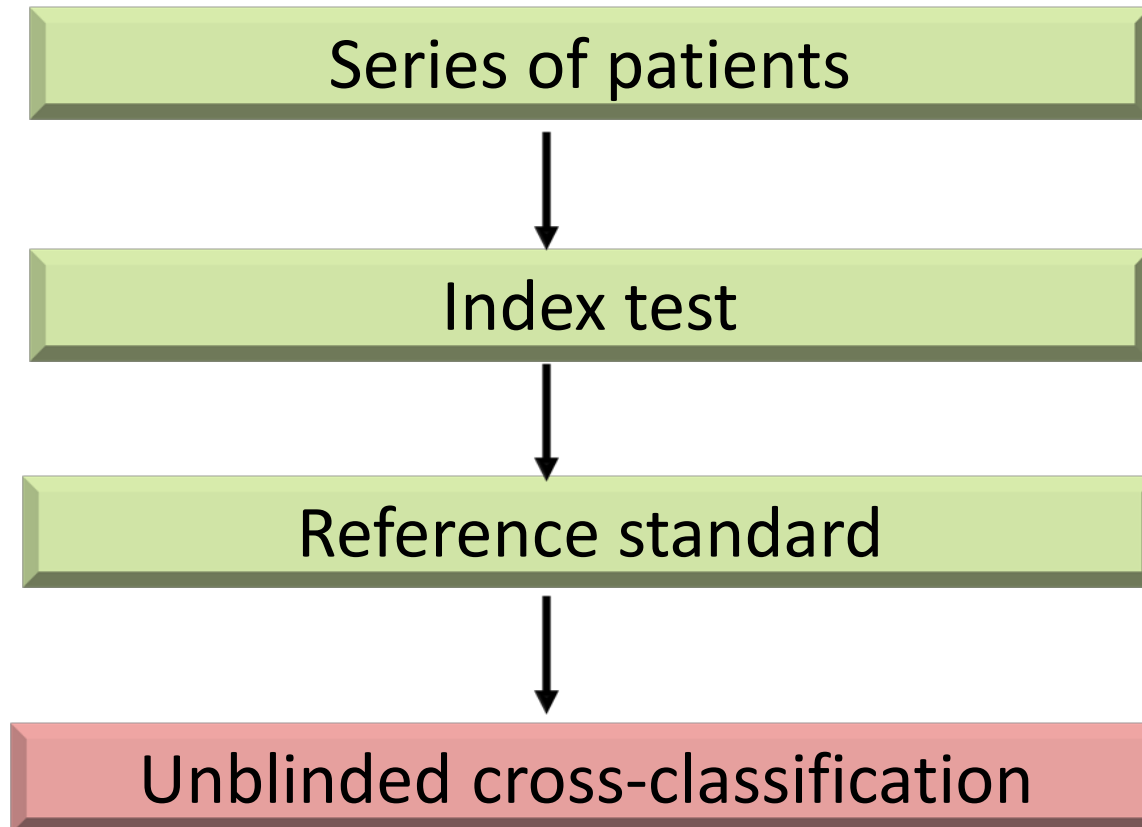


#### **Observer bias:**

test is very subjective, or  
done by person who knows  
something about the  
patient or samples

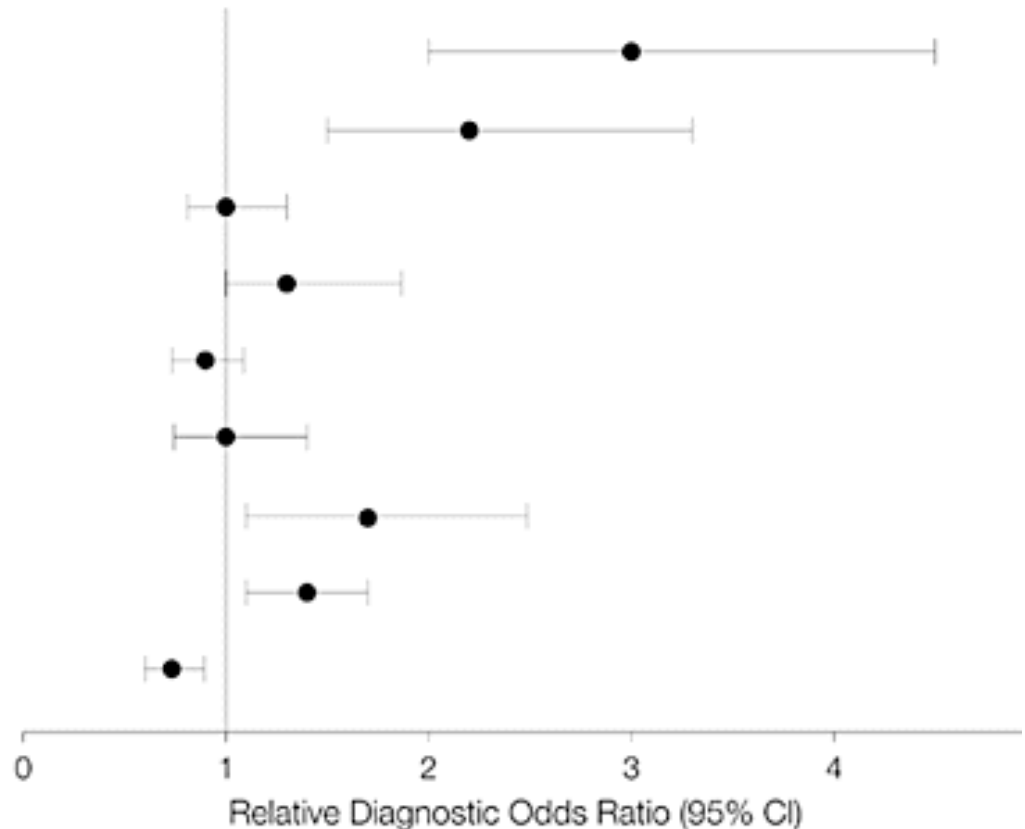


# Observer Bias



# Effect of biases on results

Study Characteristics	Relative Diagnostic Odds Ratio (95% CI)
Case-Control	3.0 (2.0-4.5)
Different Reference Tests	2.2 (1.5-3.3)
Partial Verification	1.0 (0.8-1.3)
Not Blinded	1.3 (1.0-1.9)
Nonconsecutive	0.9 (0.7-1.1)
Retrospective	1.0 (0.7-1.4)
No Description Test	1.7 (1.1-2.5)
No Description Population	1.4 (1.1-1.7)
No Description Reference	0.7 (0.6-0.9)





# 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

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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.<sup>1</sup> 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 a precise diagnosis in primary care is to use a near

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Total	61	96	157



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1. Spectrum

2. Index test

3. Reference 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  $-80^{\circ}\text{C}$ . 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



# The Numbers



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# Appraising diagnostic tests

Are the results valid?

- Appropriate spectrum of patients?
- Does everyone get the reference 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?



9 March 2014 Last updated at 18:13



## Blood test can predict Alzheimer's, say researchers

By James Gallagher

Health and science reporter, BBC News



**A blood test can accurately predict the onset of Alzheimer's disease, according to US researchers.**

They showed that testing levels of 10 fats in the blood could predict - with 90% accuracy - the risk of the disease coming on in the next three years.

Their findings, [published in Nature Medicine](#), will now be tested in larger clinical trials.

Experts said the results needed to be confirmed, but such a test would be "a real step forward".

The number of people living with dementia stands at 44 million around the globe and is expected to treble by 2050.

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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

		Disease	
		+	-
Test	+	True positives	False positives
	-	False negatives	True negatives





# Sensitivity and Specificity



# The 2 by 2 table: Sensitivity

		Disease	
		+	-
Test	+	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

$$\text{Sensitivity} = a / a + c$$

$$\text{Sensitivity} = 84/100$$



# The 2 by 2 table: Specificity

		Disease	
		+	-
Test	+		25 b False positives
	-		75 d True negatives

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

$$\text{Specificity} = d / b + d$$

$$\text{Specificity} = 75/100$$



# The Influenza Example

Disease: Lab Test

		+	-	
Test: Rapid Test	+	27	3	30
	-	34	93	127
		61	96	157

*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).



# Predictive Values



# Positive and Negative Predictive Value

		Disease	
		+	-
Test	+	a True positives	b False positives
	-	c False negatives	d True negatives

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

$$\text{PPV} = a / a + b$$

$$\text{NPV} = d / c + d$$

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





# The Influenza Example

Disease: Lab Test

		+	-	
Test: Rapid Test	+	27	3	30
	-	34	93	127
		61	96	157

PPV =  $27/30 = 90\%$

NPV =  $93/127 = 73\%$



# Predictive Value: Natural Frequencies

Your father went to his doctor and was told that his test for a disease was positive. He is really worried, and comes to ask you for help!



After doing some reading, you find that for men of his age:

The prevalence of the disease is 30%

The test has a sensitivity of 50% and specificity of 90%

*“Tell me what’s the chance I have this disease?”*



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# Predictive Value



Disease has a prevalence of 30%.

The test has sensitivity of 50% and specificity of 90%.

- 100%

Likely

- 50%

Maybe

- 0%

Unlikely



# Natural Frequencies



Disease has a prevalence of 30%.

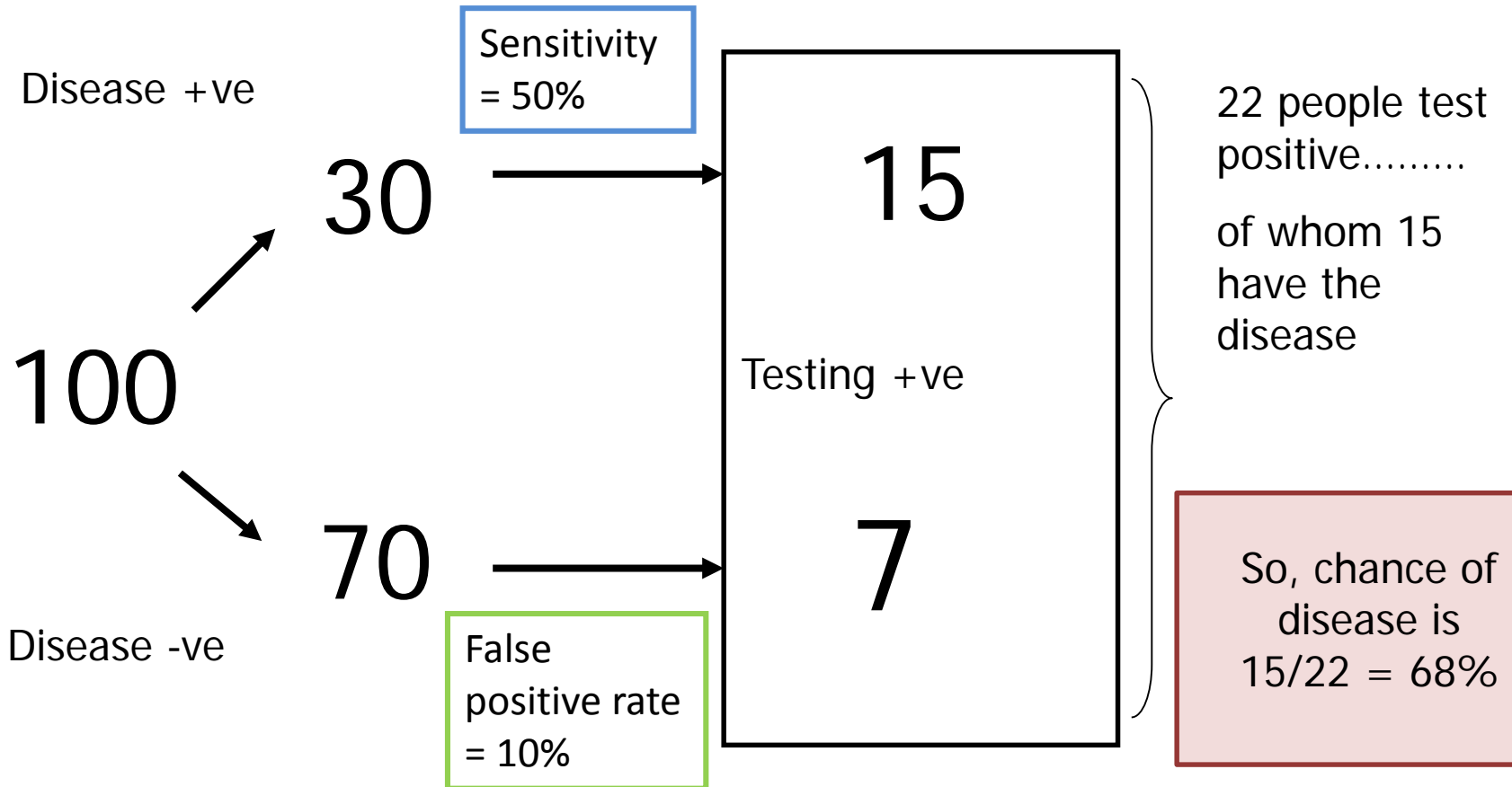
The test has sensitivity of 50% and specificity of 90%.

Given a positive test, what is the probability your dad has the disease

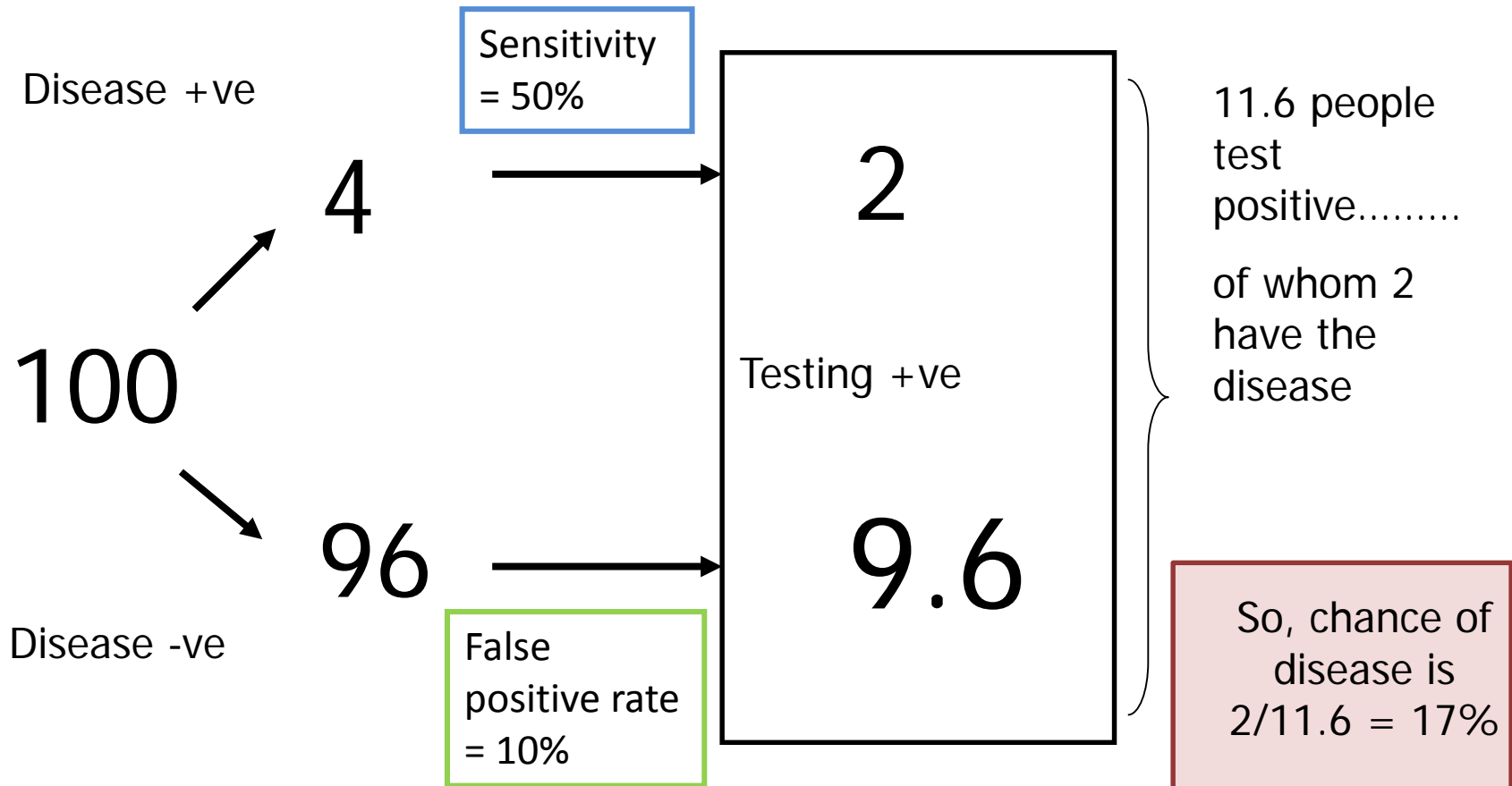
End



# Prevalence of 30%, Sensitivity of 50%, Specificity of 90%



# Prevalence of 4%, Sensitivity of 50%, Specificity of 90%



# 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 with the disease and the number of patients without the disease is equivalent to the prevalence** of the diseases in the studied population
- Use Likelihood Ratio - does not depend on prevalence





# Likelihood Ratios



# Likelihood ratios

$$\text{LR} = \frac{\text{Probability of clinical finding in patients with disease}}{\text{Probability of same finding in patients without disease}}$$



# 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?

$$\text{LR+} = \text{sens} / (1 - \text{spec})$$

## Negative likelihood ratio (LR-)

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

$$\text{LR-} = (1 - \text{sens}) / \text{spec}$$



# What do likelihood ratios mean?

LRs = Diagnostic Weights

Probability

decrease

increase

-45%

-30%

-15%

+15%

+30%

+45%

LRs

0.1

0.2

0.5

1

2

5

10

LRs

LR < 0.1 = strong  
negative test  
result

LR = 1

No diagnostic  
value

LR > 10 = strong  
positive test  
result



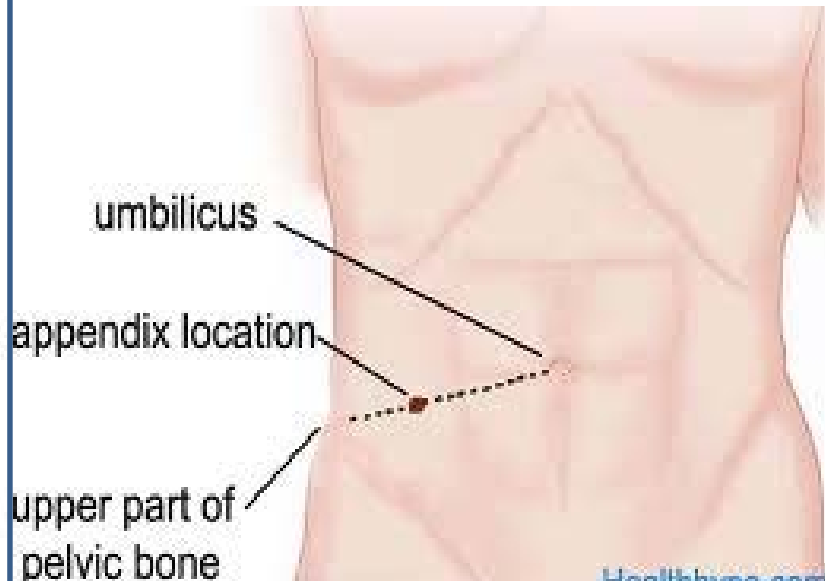
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# Diagnosis of Appendicitis

## 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

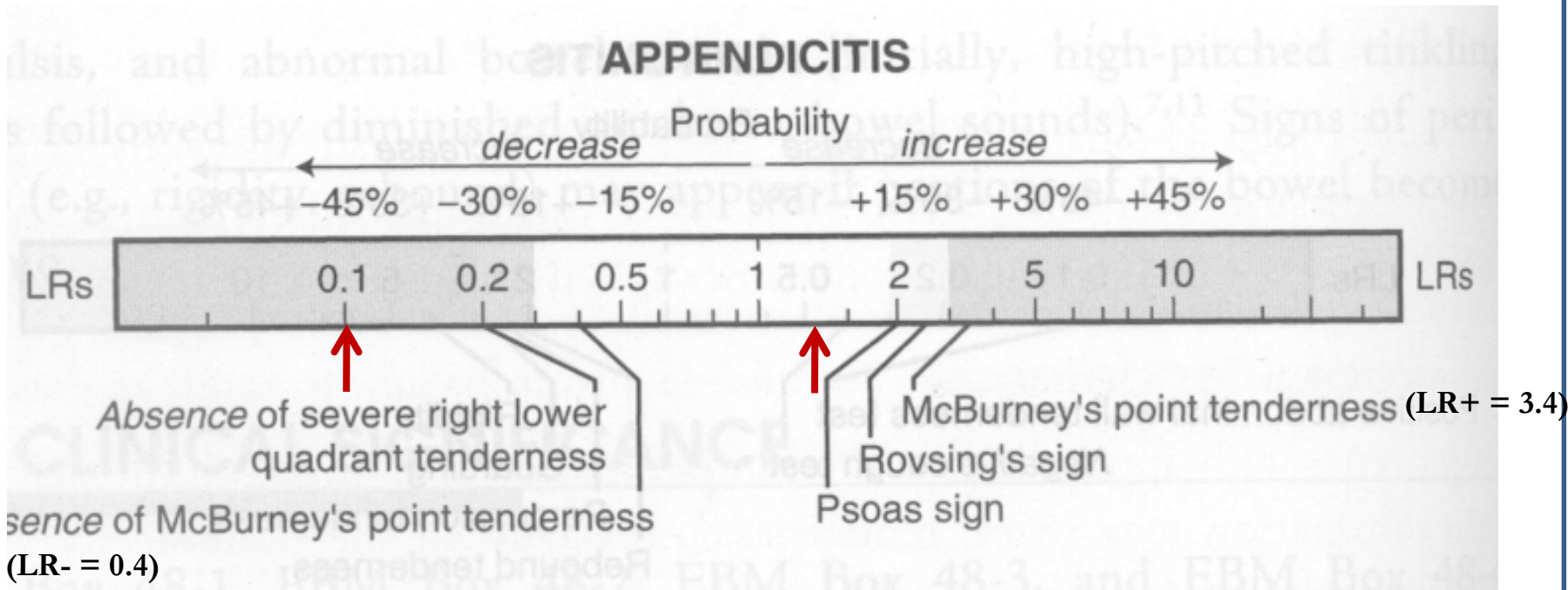
Abdominal pain resulting from passively extending the thigh of a patient or asking the patient to actively flex his thigh at the hip

## Ashdown's sign

Pain when driving over speed bumps



# For Example



Speed bump test (Ashdown's sign):

LR+ = 1.4

LR- = 0.1

# Beyond Test Accuracy....



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# 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?



**What about the news story...?**



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A loo with a view!  
Builder spends

'Plastered' former  
deputy speaker

Soldier, 32,  
'murdered' at British

Britain to bask in a  
WEEK of sunshine

Does your breath  
smell like nail polish

Will climate change  
bring back

Mum  
touch

## Blood test that can predict Alzheimer's: Elderly could be given early warning

- The simple blood test could give early warning within three years
- The test could speed the search for new drugs that delay or prevent disease
- Experts are pleased, but it could bring health concerns if no cure is found

By **FIONA MACRAE** SCIENCE CORRESPONDENT

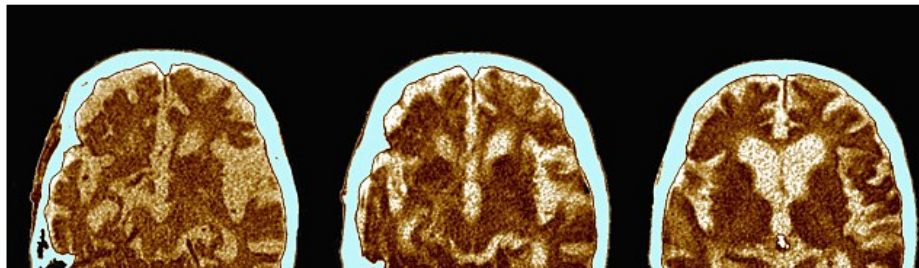
PUBLISHED: 19:40, 9 March 2014 | UPDATED: 09:43, 10 March 2014

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A simple blood test has been developed that gives healthy elderly people precious early warning they may get Alzheimer's within the next three years.

It is hoped the test, the first to predict accurately who will become ill, could speed the search for new drugs that can delay or even prevent the devastating brain disease.

It could eventually lead to widespread screening in middle-age to identify those most at risk and give them greater warning.




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# Plasma phospholipids identify antecedent memory impairment in older adults

Mark Mapstone<sup>1</sup>, Amrita K Cheema<sup>2,3</sup>, Massimo S Fiandaca<sup>4,5</sup>, Xiaogang Zhong<sup>6</sup>, Timothy R Mhyre<sup>5</sup>, Linda H MacArthur<sup>5</sup>, William J Hall<sup>7</sup>, Susan G Fisher<sup>8,14</sup>, Derick R Peterson<sup>9</sup>, James M Haley<sup>10</sup>, Michael D Nazar<sup>11</sup>, Steven A Rich<sup>12</sup>, Dan J Berlau<sup>13,14</sup>, Carrie B Peltz<sup>13</sup>, Ming T Tan<sup>6</sup>, Claudia H Kawas<sup>13</sup> & Howard J Federoff<sup>4,5</sup>

Sensitivity: 90%  
Specificity: 90%

Leading the fight  
against dementia

Alzheimer's  
Society

Dementia Prevalence:  
1.3% of the entire UK population  
7% of the UK population over 65



# Natural Frequencies

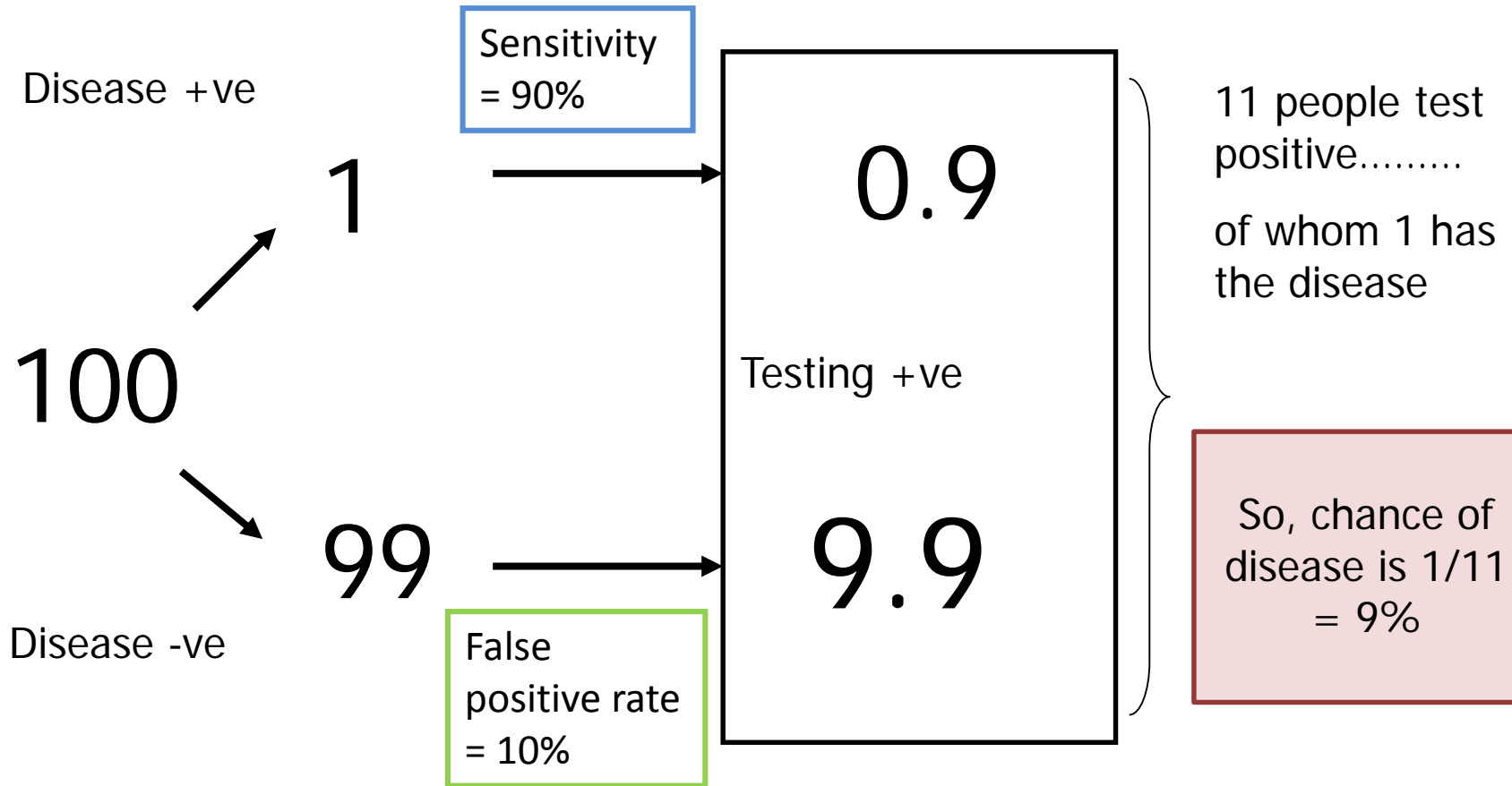


Dementia has a prevalence of 1%.  
The test has sensitivity of 90% and specificity of 90%.  
Given a positive test, what is the probability the person has "preclinical" Alzheimer's?

End

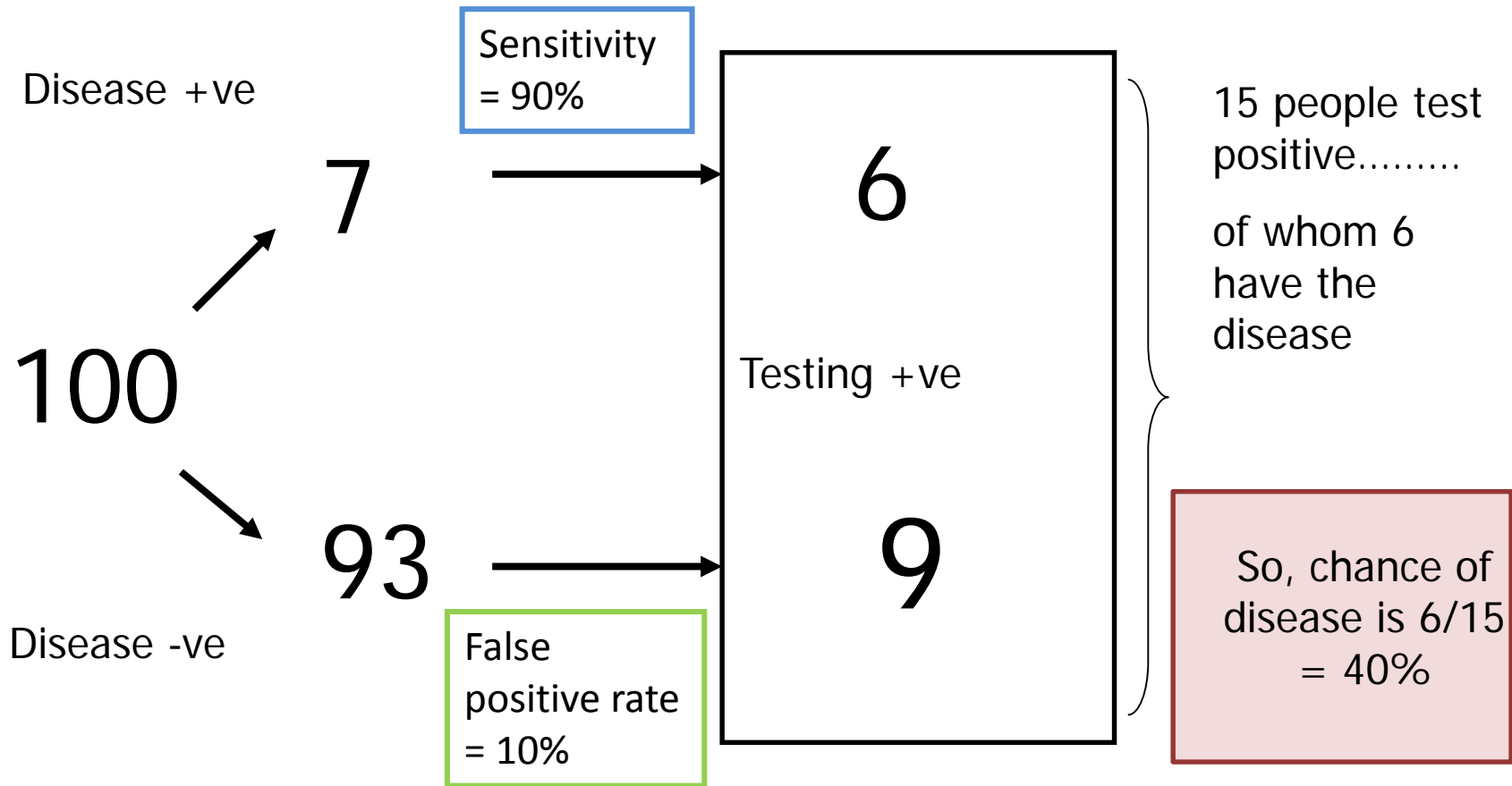


# Prevalence of 1%, Sensitivity of 90%, Specificity of 90%



Over 65 years:

Prevalence of 7%, Sensitivity of 90%, Specificity of 90%



Researcher Howard Federoff took blood samples from hundreds of healthy men and women aged 70-plus. During the next five years, some developed Alzheimer's. Their blood samples were then compared with the samples taken from the people who remained free of the disease.

This flagged up a battery of seven fats that were present in lower amounts in the blood of those who went on to develop memory problems – despite them appearing healthy at the time they gave blood. Dr Federoff then confirmed the finding on a second group.

Writing in the journal *Nature Medicine*, he said the test can give two to three years' warning of Alzheimer's with 90 per cent accuracy. He said it is the first blood test to accurately forecast if an apparently healthy person will succumb to Alzheimer's. It is also quicker, cheaper and less invasive than other methods such as expensive scans and painful lumbar punctures.

It isn't entirely clear how the test works but changes in the blood may be a sign of brain cells deteriorating even when people appear healthy.

Dr Simon Ridley, of Alzheimer's Research UK, said: 'More work is needed to confirm these findings, but a blood test to identify people at risk of Alzheimer's would be a real step forward for research.'

Dr Doug Brown, of the Alzheimer's Society, said: 'Having such a test would be an interesting development, but it also throws up ethical considerations. If this does develop in the future people must be given a choice about whether they would want to know, and fully understand the implications.'







It makes business sense. [Find out more](#)

0:52 / 1:11

## The 'breakthrough' iPad game that can spot autism in children with **93%** accuracy

- Gave 33 children with autism and 45 without iPad games to play
- Games were coded with ability to track finger movements and gestures
- Following the gameplay, the team analyzed data from both groups
- Found children with autism have a greater force of impact than others

By STACY LIBERATORE FOR DAILYMAIL.COM

PUBLISHED: 00:21, 31 August 2016 | UPDATED: 14:58, 31 August 2016



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The way children play iPad games could reveal if they have autism, researchers have found.

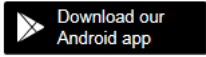
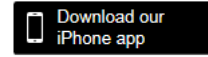
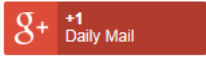
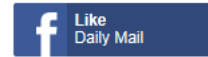
They found those with the condition used greater force and moved their finger in different ways.

It is hoped the app could lead to earlier diagnosis and treatment.

Scroll down for video

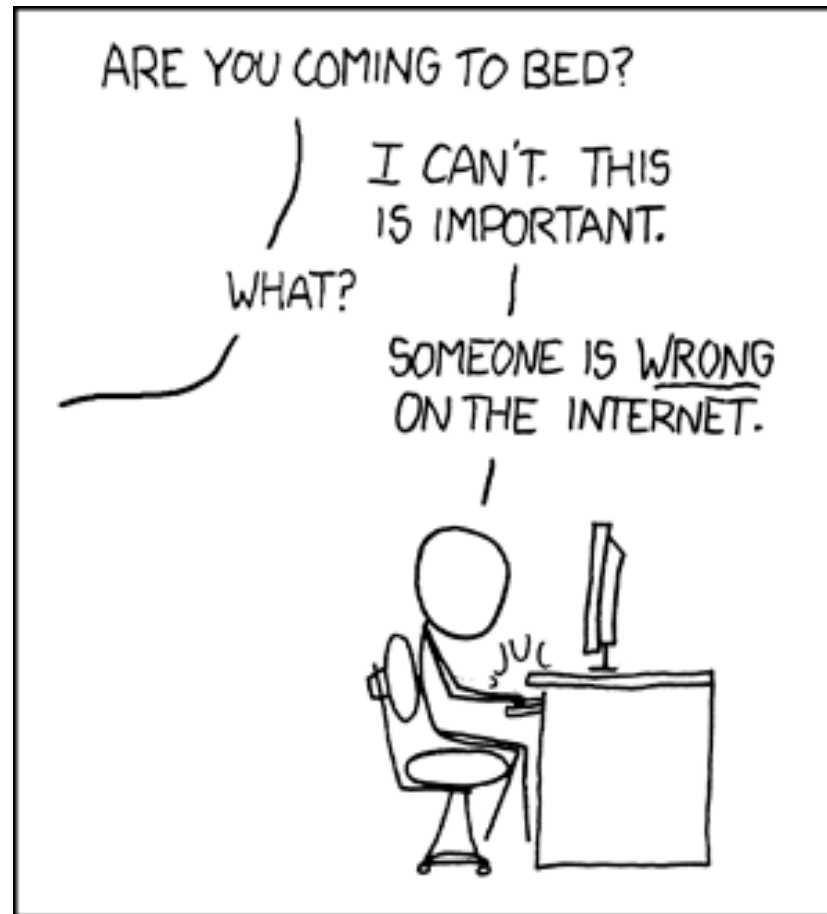


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[www.xkcd.com](http://www.xkcd.com)



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

Are the results valid?

```
graph TD; A[Are the results valid?] --> B[What are the results?]; B --> C[Will they help me look after my patients?];
```

What are the results?

Will they help me look  
after my patients?

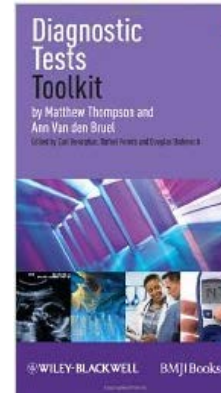
**Don't believe everything you are told,  
Ask for the Evidence!**



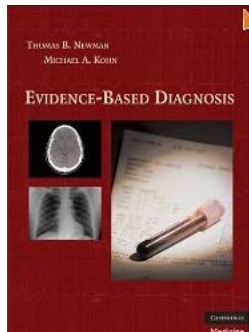
# Useful books on diagnostics



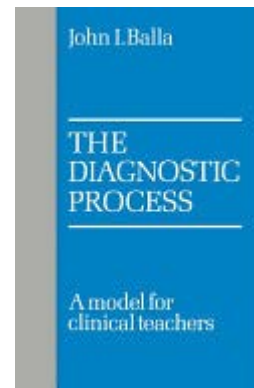
Evidence based  
Physical Diagnosis.  
Steven McGee.  
Saunders



Diagnostic Tests Toolkit.  
Thompson & Van den Bruel.  
Wiley-Blackwell.



Evidence-based  
Diagnosis.  
Newman & Kohn.  
Cambridge Univ. Press



The Diagnostic Process.  
John Balla.  
Cambridge Univ. Press



Evidence base of Clinical  
Diagnosis.  
Knottnerus & Buntinx.  
Wiley-Blackwell

# Useful journal articles on diagnostics

- Bossuyt. Additional patient outcomes and pathways in evaluations of testing. *Med Decis Making* 2009
- Heneghan et al. Diagnostic strategies used in primary care. *BMJ* 2009
- Ferrante di Ruffano. Assessing the value of diagnostic tests: a framework for designing and evaluating trials. *BMJ* 2012
- Mallett et al. Interpreting diagnostic accuracy studies for patient care. *BMJ* 2012
- Bossuyt et al. STARD initiative. *Ann Int Med* 2003
- Lord et al. Using principles of RCT design to guide test evaluation. *Med Decis Making* 2009
- Rutjes et al. Evidence of bias and variation in diagnostic accuracy studies. *CMAJ* 2006
- Lijmer et al. Proposals for phased evaluation of medical tests. *Med Decis Making* 2009
- Whiting et al. QUADAS-2: revised tool for quality assessment of diagnostic accuracy studies. *Ann Int Med* 2011
- Halligan S, Altman DG, Mallett S. Disadvantages of using the area under the receiver operating characteristic curve to assess imaging tests: A discussion and proposal for an alternative approach. *Eur Radiol.* 2015



