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WHAT IS WRONG WITH MY PATIENT? HOW TO READ AN ARTICLE CONCERNING DIAGNOSIS

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Two critically important questions arise from the doctor-patient encounter. Firstly, given the patient's profile (demography, signs and symptoms), what is the most likely diagnosis, and secondly given the diagnosis what is the most effective intervention?

Diagnostic reasoning skills are vital for effective patient care. The basis of these skills should be sound diagnostic research on the appropriate signs, symptoms and tests regarding a particular disease. Diagnostic research has undergone significant developments during the last number of years. Some of these principles are common knowledge while others are poorly understood. Given that diagnostic knowledge is vital for patient care it is imperative that the practising physician should be able to appraise articles on diagnostic research critically.

The development of diagnostic research has been a stepwise refinement of concepts (Fig.1).

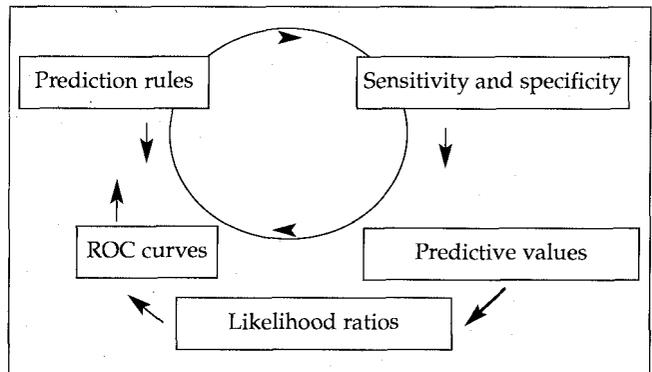


Fig. 1. Progressive steps in diagnostic research.

STEPS IN DIAGNOSTIC RESEARCH

Sensitivity and specificity

	Disease + (D ⁺)	Disease - (D ⁻)
Test + (T ⁺)	a	b
Test - (T ⁻)	c	d

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The sensitivity of a test is typically given as $a/(a + c)$. This can be translated into the probability of finding a test positive given a certain disease: $P(T^+/D^+)$. Specificity is $d/(d + b)$ or $P(T^-/D^-)$. Reporting the sensitivity and specificity of a test can be helpful as a negative Sensitive test rules out disease (SNOUT) and a positive Specific test rules in disease (SPIN).¹ There is always a trade-off between sensitivity and specificity. The higher the sensitivity the lower the specificity and vice versa (later illustrated with Receiver Operating Characteristic (ROC) curves).²

In principle the diagnostician is not interested to know how the test will perform given a diseased or disease-free patient. The disease status of the patient is his prime concern and therefore the diagnostician is interested in $P(D^+/T^+)$ or $P(D^-/T^-)$, that is, the probability of disease or not given a particular test result. This leads to the concept of positive predictive value (PPV) or negative predictive value (NPV).

Predictive values²

	Disease + (D ⁺)	Disease - (D ⁻)
Test + (T ⁺)	a	b
Test - (T ⁻)	c	d

The PPV $P(D^+/T^+)$ is given by $a/(a + b)$, and the NPV $P(D^-/T^-)$ by $d/(c + d)$. These values are clearly useful as a PPV of, e.g. 80%, will imply that given a positive test result the diagnostician can be 80% certain that the patient has the disease being tested for.

However, the value of using predictive values is markedly affected by the prevalence of the disease.² Another term often used for prevalence is pre-test probability. If the prevalence of hypertension in a population of men between the ages of 40 and 60 years is 20%, then the probability of finding hypertension even before you take the blood pressure will be 20% in a man in that age category.

Hypothetical example: Test for predicting pancreas carcinoma						
	D ⁺	D ⁻	D ⁺	D ⁻	D ⁺	D ⁻
T ⁺	610	58	436	96	174	150
T ⁻	90	242	64	404	76	650
Prevalence	Prevalence		Prevalence			
= 0.7 (70%)	= 0.5 (50%)		= 0.2 (20%)			
PPV = 0.92	PPV = 0.82		PPV = 0.54			
NPV = 0.73	NPV = 0.86		NPV = 0.96			

The PPV will decrease as the prevalence decreases and the NPV will increase. The reverse is true when the prevalence increases. This is one of the severe limitations of screening tests. Screening is usually done in a low-prevalence setting

with a subsequent low PPV following a positive screening test. It should be appreciated that a low PPV implies a high false-positive rate. This may lead to unnecessary, expensive, sometimes painful or even harmful follow-up testing.

The following example demonstrates some of these principles. A patient presenting with jaundice to a specialised liver clinic may have a pre-test probability (given the special interest of the clinic) for primary biliary cirrhosis (PBC) as high as 40%. A positive serological test may therefore have a high PPV for PBC. If, after the liver clinic, one was to see a jaundiced patient at the general outpatient clinic, one would again order the same serological test. Now the PPV will be much less because the prevalence of PBC will be much lower in this clinic and the diagnosis of hepatitis A or B much more likely.

Because of the limitation set by the prevalence of the disease, a likelihood ratio (LR) might be a better parameter than predictive values.

Likelihood ratio²

A potential benefit of the LR is that it is not dependent on the prevalence of disease.

	Disease + (D ⁺)	Disease - (D ⁻)
Test + (T ⁺)	a	b
Test - (T ⁻)	c	d

A positive LR is the likelihood of finding a test positive in someone diseased compared with the likelihood of finding a test positive in someone without the disease: $(a/a + c)/(b/d + b) = (sens/1 - spec)$. A negative LR is $(1 - sens/spec)$.

For example, if a test has a positive LR of 18 it implies that a diseased person will be 18 times more likely to have a positive test than a person without the disease.

Even though this may be seen as an improvement, LRs have some limitations. An LR cannot be translated into a probability. ('Mrs Smith I am not certain as to what the exact probability is that you have a lung embolus, but I can say that if you did not have a lung embolus you would have been 18 times less likely to have tested positive with this test!')

Diagnostic tests are often dichotomised into positive and negative. The cut-off is often based at a level at which both the sensitivity and specificity are at their highest. The relationship between sensitivity and specificity is well illustrated with the use of ROC curves (Fig. 2). The area under the curve represents the ability of the test to distinguish between diseased and non-diseased states. The diagonal line yields an area below of 0.50 (50%), i.e. the test has no better predictive ability than flipping a coin. When comparing two diagnostic tests, the test with a curve closest to the left upper corner is the better test. The cut-off nearest to the upper left corner also represents the best trade-off between sensitivity and specificity and this point is often chosen as a cut-off for dichotomising tests.

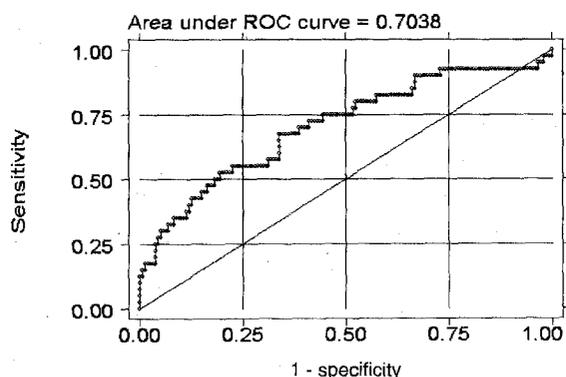


Fig. 2. Receiver Operating Characteristic ROC curve.

An important concept in diagnostic research which is often used subconsciously by the astute clinician is Bayes theorem — the post-test odds of having a disease = pre-test odds \times the LR of the positive test. Remember that odds = (probability/1 - probability). If the pre-test probability (prevalence) before testing is 40%, then the odds are $(0.4/1 - 0.4) = 0.66$. If the LR for a positive test is 5, then the post-test odds are 3.3 and this translates to a post-test probability of $(3.3/1 + 3.3) = 0.77 = 77\%$. Where we were only 40% sure of the diagnosis before testing we are now 77% sure. Depending on the disease this probability may be high enough to start treatment, or if treatment is potentially harmful and more certainty is required another test may be used. These difficult calculations can be avoided by using Fagan's nomogram³ which can be found at <http://cebm.jr2.ox.ac.uk/docs/nomogram.html>

Using this approach it can be appreciated why the good clinician does not do a diagnostic test (such as a stress electrocardiogram (ECG)) on a 20-year-old female patient with atypical chest pain. The pre-test probability of ischaemic heart disease is so low that the diagnostic test would have to have an exceptionally high positive LR (+ LR) to change the pre-test probability from 15% to 80%. The same reasoning holds why it is illogical to do a stress test on a 65-year-old diabetic hypertensive male with typical angina. The pre-test probability is already 80% or more and even a negative test won't reduce this by much and a positive test would only increase this probability marginally (you might want to do a stress test for prognostic reasons).

Another use for LRs is to use different cut-off values for a test and to give the LR for each cut-off (Table I). Useful comments regarding LRs can be found at <http://cebm.jr2.ox.ac.uk/docs/likerats.html> and <http://www.med.ualberta.ca/ebm/ebm.htm> (Table II). An LR greater than 1 produces a post-test probability which is higher than the pre-test probability. An LR less than 1 produces a post-test probability which is lower than the pre-test probability. When the pre-test probability lies between 30% and 70%, test results with a very high LR (say, above 10) rule in disease. An LR

Table I. Use of likelihood ratios at different cut-off values for diagnosing acute pancreatitis

Use of a novel (hypothetical) marker	Likelihood ratio
> 20 mmol/l	+LR 10
15 - 20 mmol/l	+LR 6
10 - 14.9 mmol/l	+LR 2
5 - 9.9 mmol/l	+ LR 0.8
1 - 4.9 mmol/l	+ LR 0.2

Table II. How much do likelihood ratios (LRs) change disease likelihood?

- LRs > 10 or < 0.1 cause large changes in likelihood
- LRs 5 - 10 or 0.1 - 0.2 cause moderate changes
- LRs 2 - 5 or 0.2 - 0.5 cause small changes
- LRs between 2 and > 0.5 cause little or no change
- LRs of 1.0 cause no change at all

below 1 produces a post-test probability less than the pre-test probability. A very low LR (say, below 0.1) virtually rules out the chance that the patient has the disease.

The LR assumes that sensitivity and specificity are stable test characteristics. However, this is not always the case. Severity of disease greatly influences these test characteristics. A useful example is visual inspection of abdominal girth for diagnosing pregnancy. This would be a very poor test early in pregnancy but a very good test at 9 months' gestation! This has been shown to be the case in many circumstances ranging from cancer to deep venous thrombosis.⁴⁵

The biggest drawback in the evaluation of diagnostic tests up to this point has been that the test has been used singularly to rule a disease in or out. This is very seldom the case in clinical practice and is probably only done when applying screening tests.

In general the clinician uses demographic characteristics, history, physical signs and special investigations to confirm a diagnosis. Therefore the most valuable technique for appraising diagnostic tests would take this into account.

Logistic regression and prediction rules^{6,7}

The astute clinician knows that a disease is never diagnosed with 100% certainty. Once a certain threshold of probability is passed the patient is either sent home or admitted to the intensive care unit! This is very well simulated by a logistic regression curve. The probability of disease lies between 0 and 1 in a non-linear fashion. Logistic regression may seem difficult to comprehend but the principles are quite straightforward.

Leaving the statistical notation aside, the logistic function describes the probability that the disease in question is present given certain clinical parameters such as a certain age, gender, pain characteristic, etc.



Example 1 — diagnosing a pulmonary embolus

Probability of a pulmonary embolus =

$$\frac{1}{1 + e^{-(a + b_1(\text{age}) + b_2(\text{gender}) + b_3(\text{haemoptysis}))}}$$

where a is the intercept and b the regression coefficient. So given a certain age, gender and the absence or presence of haemoptysis, we can predict the probability of a pulmonary embolus.

One of the most useful characteristics of logistic regression is that e^b = odds ratio. For example, from your computer output you find that the beta coefficient for age = 0.2. This means that for each year increase in age you are $e^{0.2} = 1.2$ times more likely to have a pulmonary embolus, or more usefully, for every decade increase in age you are $e^2 = 7.4$ times more likely to have a pulmonary embolus than someone a decade younger.

With logistic regression (bearing in mind all the various steps and assumptions) it is possible to use as much information as is available to make the diagnosis. For example, age, gender, ethnic group, pulse, temperature, pleuritic pain (yes or no), haemoptysis (yes or no), pleural rub (yes or no), abnormal chest radiograph (yes or no), abnormal ventilation perfusion scan (yes or no).

What is also often done is to follow the stepwise approach the clinician normally takes in his diagnostic reasoning.

1. Using data obtained from history only, a logistical function is derived. Many statistical packages such as Stata[®] can then perform a ROC analysis with an area under the curve estimate (Fig. 2).

2. By adding findings from the clinical examination a new model can be estimated and an ROC curve drawn. If the clinical examination is useful at all the area under the curve will improve with statistical significance.

3. The same can now be done with the added information provided by the special investigations.

After the final logistic regression model has been obtained the coefficients are often changed into scores to make the regression function more meaningful as a whole (clinical prediction rule). An example is the Framingham cardiovascular risk equation⁹ (here the outcome is the risk of ischaemic heart disease).

Example 2 — prediction of bacteraemia (positive blood cultures)¹⁰

As an intern it would be useful to know beforehand what the probability would be of obtaining a positive blood culture in any given patient with fever in the ward (especially after 10 at night!). Examples of the variable used to derive the risk score are given in Table III.

From Table IV the intern knows that if the score is less than 3 there is a 99% probability that blood cultures will come back negative (all that's left is to convince his consultant that blood cultures are unnecessary!).

Table III. Certain of the variables used for predicting bacteraemia*

	Beta	Odds ratio	Score
Maximum			
temperature > 38.3°C	0.91	2.5	3
Rapidly fatal disease	1.40	4	4
Chills present	0.96	2.6	3

* Adapted with permission from Bates *et al.*¹⁰

Table IV. Risk score for predicting bacteraemia*

Risk score	0 - 2	3	4 - 5	≥ 6
P/(Bacteraemia absent)	99%	95%	91%	84%
P/(Bacteraemia present)	1%	5%	9%	16%

* Adapted with permission from Bates *et al.*¹⁰

Table V. Evaluating an article on diagnostic research^{14,15}

Is the study valid?

1. Was there an independent, blind comparison with a reference (gold) standard of diagnosis?
2. Was the diagnostic test evaluated in an appropriate spectrum of patients (such as those in whom it would be used in practice)?
3. Was the reference standard applied regardless of the diagnostic test result? (avoiding verification bias)
4. Were the test's methods described clearly enough to permit replication?

What are the results and their level of precision?

1. In what form are the results given and how useful are they? (sensitivity/specificity, predictive values, likelihood ratios, odds ratios)
2. Are confidence intervals provided around these mean estimates?

Can I use these results in clinical practice?

1. Will the test be reproducible and well interpreted in my practice setting?
2. Are the results applicable to my patients?
3. Will the test results change my management?
4. Will my patients be better off because of the test?

A number of prediction rules have been developed recently, with the Ottawa ankle rule^{11,12} and the Framingham risk equation¹⁰ among the most quoted. A number of these will be developed in future and the diagnostician will have to learn how to appraise these rules. One of the fundamental principles that needs to be adhered to is that the rule is usually developed in one population and validated in another. This is critical in order to make the rule generalisable. Often a diagnostic rule works well in the population in which it is developed, but then performs poorly when validated. Also important is that for logistic regression a large group of patients is usually required, at least 10 positive cases for each variable explored (and probably more)^{16,13}. So beware of odds ratios that have been



derived from a dataset of 50 subjects of whom 10 had the disease in question. Further guidelines for the evaluation of decision rules are provided in reference 7.

Rules for interpreting diagnostic literature are given in Table V.^{14,15} It is useful to remember that the following principles apply to all medical literature: (i) is the study valid?; (ii) what are the results and their level of precision?; (iii) can I apply these results in my practice?

Diagnostic research is still in its infancy and the clinician can look forward to better ways of overcoming uncertainty regarding ruling disease in or out. However, it is imperative that the clinician understands and applies the principles related to diagnostic research and reasoning in order to ensure optimal patient management.

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PREVALENCE OF PRE-CANCEROUS LESIONS AND CERVICAL CANCER IN SOUTH AFRICA — A MULTICENTRE STUDY

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Objectives. To describe the age-specific prevalence rates of cancer of the cervix in South African women presenting for screening.

Design. A multicentre prevalence survey in 10 geographically defined areas following a common core protocol. Services were located in existing service sites, with the exception of KwaZulu-Natal which used a mobile service. Women aged 20 years and above were eligible for inclusion.

Outcome measures. Age-specific cervical cytologically diagnosed abnormality rates according to the Bethesda classification.

Results. During the study 20 603 women participated. Eighty per cent of the sample had never had a Pap smear before and just over 91% had not had a Pap smear in the last 5 years. In

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