How to Read a Diagnostic Test Article

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- No conflicts of interest to report -

Information and clinical examples provided in this presentation are solely for educational purposes, and should not be substituted for clinical guidelines or up-to-date medical information.

Outline

1. Clinical decision making and role of test
2. Two x two table notation
3. Likelihood ratios and calculation of post-test probability
4. Receiver operating characteristic (ROC) curve
5. Evaluation of diagnostic test article

Clinical Decision Making

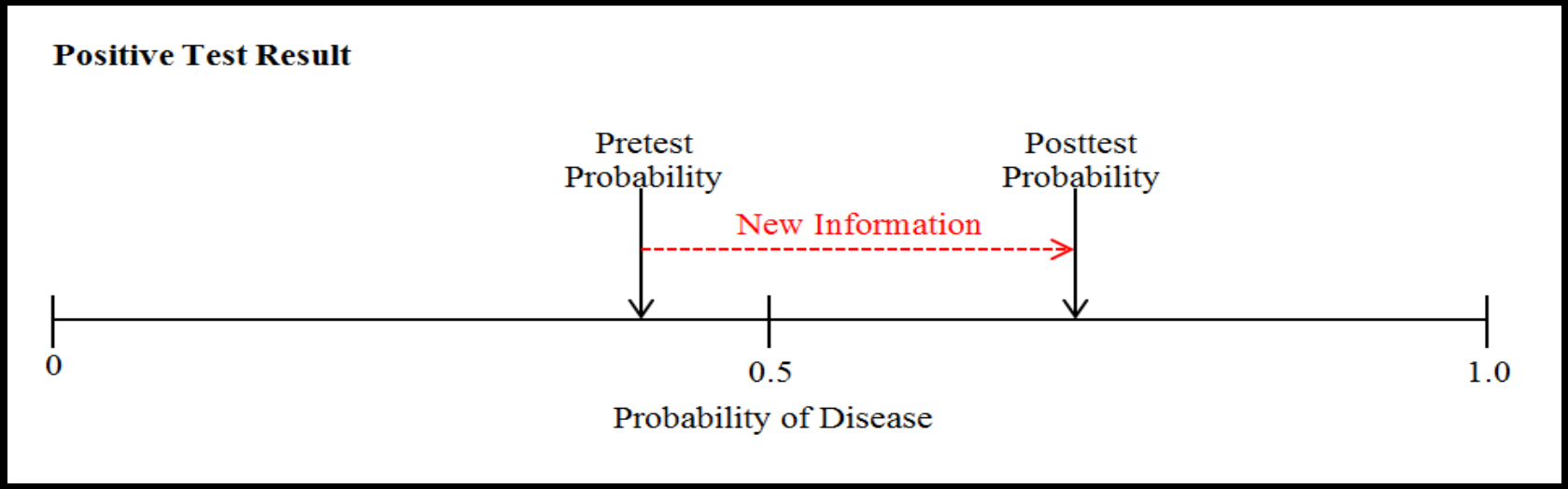
1. Clinical assessment: symptoms, signs, risk factors

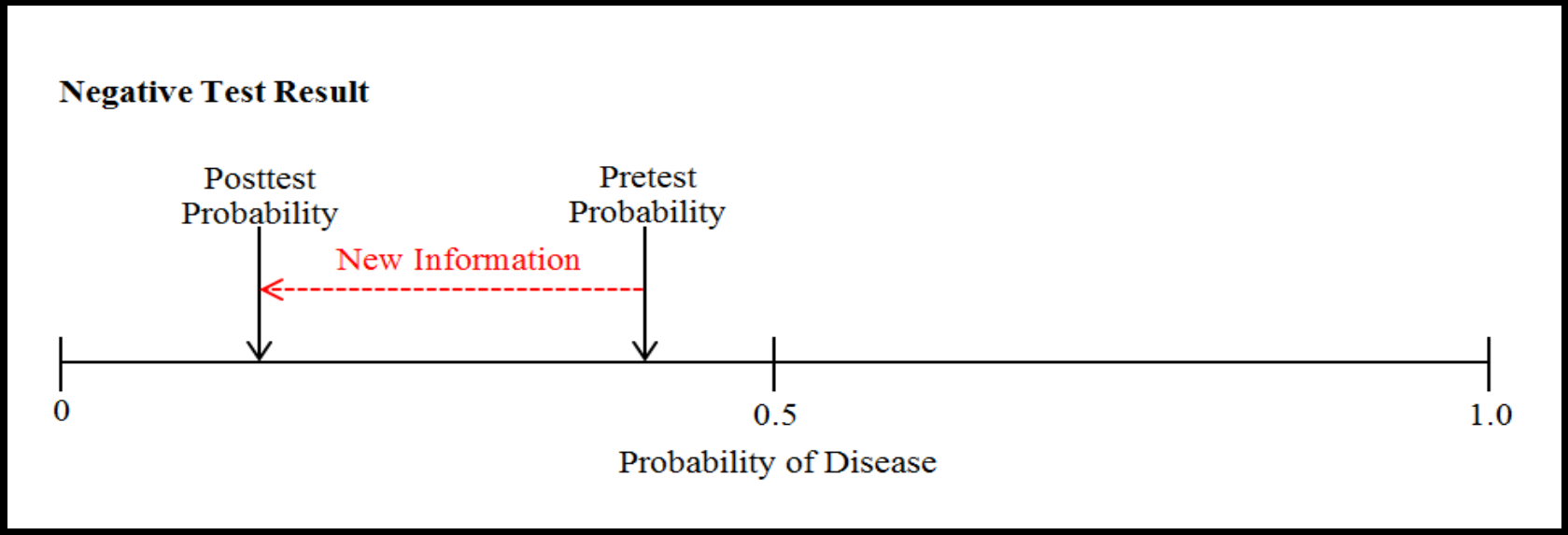
2. Estimation of disease probability…pre-test probability

3. If reasonable probability exists - order test

4. Test may increase or decrease post-test probability

Accounting for New Information





Case Vignette

Otherwise healthy 51 year-old woman presents to physician with pleuritic right posterior chest pain without dyspnea or hemoptysis.

Temperature 38.2° and pulse 102 bpm. Physical exam reveals pleural friction rub over posterior right hemithorax but patient is otherwise unremarkable. Chest radiograph is normal.

Tx: Anti-inflammatory agent for presumed viral pleurisy. Three days later, returns reporting dyspnea and slight hemoptysis. How should she be evaluated?

Question?

What is the probability of pulmonary embolism (PE) :

Low (0-20%)

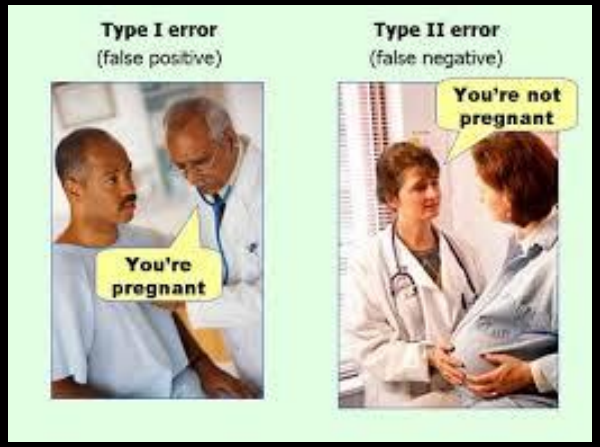
Intermediate (20-80%)

High (> 80%)

Clinical Assessment of Symptoms, Signs, Risk Factors for PE:

Simplified Wells Scoring System	
Findings	**Score***
- Clinical signs and symptoms of deep venous thrombosis (minimum of leg swelling and pain with palpation of deep veins of the leg)	3.0
- No alternate diagnosis likely or more likely than PE	3.0
- Heart rate > 100 beats/mins	1.5
- Immobilization or surgery in last 4 weeks	1.5
- Previous history of deep venous thrombosis or PE	1.5
- Hemoptysis	1.0
- Cancer actively treated w/in last 6 months	1.0
*Score calculated by summing predictor weights: Totaled scores are as follows: Low < 2; moderate 2-6; and high > 6.	

Designing a Diagnostic Test Study



1. Enroll patients with clinically suspected diagnosis – inclusion and exclusion criteria

2. Gold standard verifies disease status – determines actual probability of disease in study sample

3. Actual probability = prevalence = pretest probability of all participants

Designing a Diagnostic Test Study

4. Accuracy: total number of true positives (TP) and true negatives (TN) for test, divided by total number of tests.

5. 100% accurate test contains no false positives (FP) or false negatives (FN):

$$\frac{TP + TN}{TP + (0)FP + TN + (0)FN} \qquad \frac{TP + TN}{TP + TN} = 100\%$$

Table 2. Accuracy of Pretest Probability Assessment for Pulmonary Embolism Using Clinical Gestalt

Source	No. of Patients	Prevalence of Pulmonary Embolism, %	Category	Probability Estimate, %	No. of Patients	Actual Probability, %
PIOPED,[5] 1990	887	28	Low	0-19	228	9
			Moderate	20-79	569	30
			High	80-100	90	68

PIOPED Study (1990)[1]

Purpose: Evaluate usefulness of V/Q scan for PE

Actual PE probability: 28%

Scans read as:

- **+ High probability V/Q scan**
- **- Intermediate probability V/Q scan**
- **- Low probability V/Q scan**
- **- Normal/near normal V/Q scan**

PIOPED Study (1990)[1]

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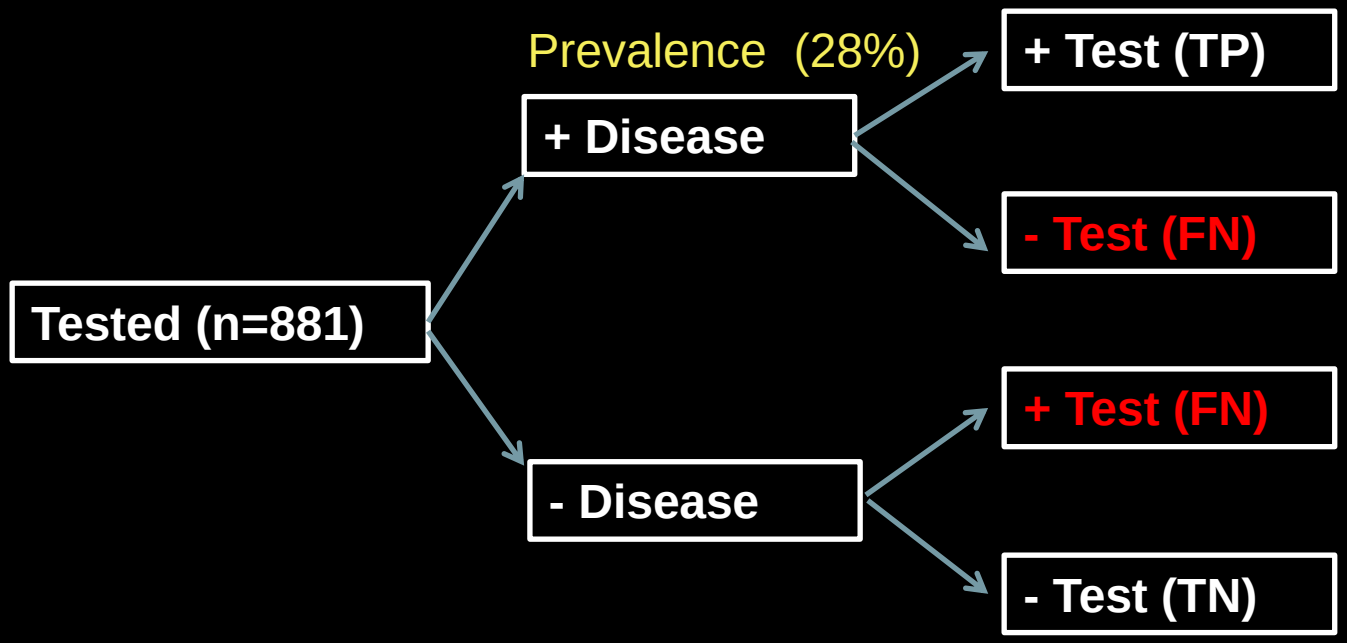
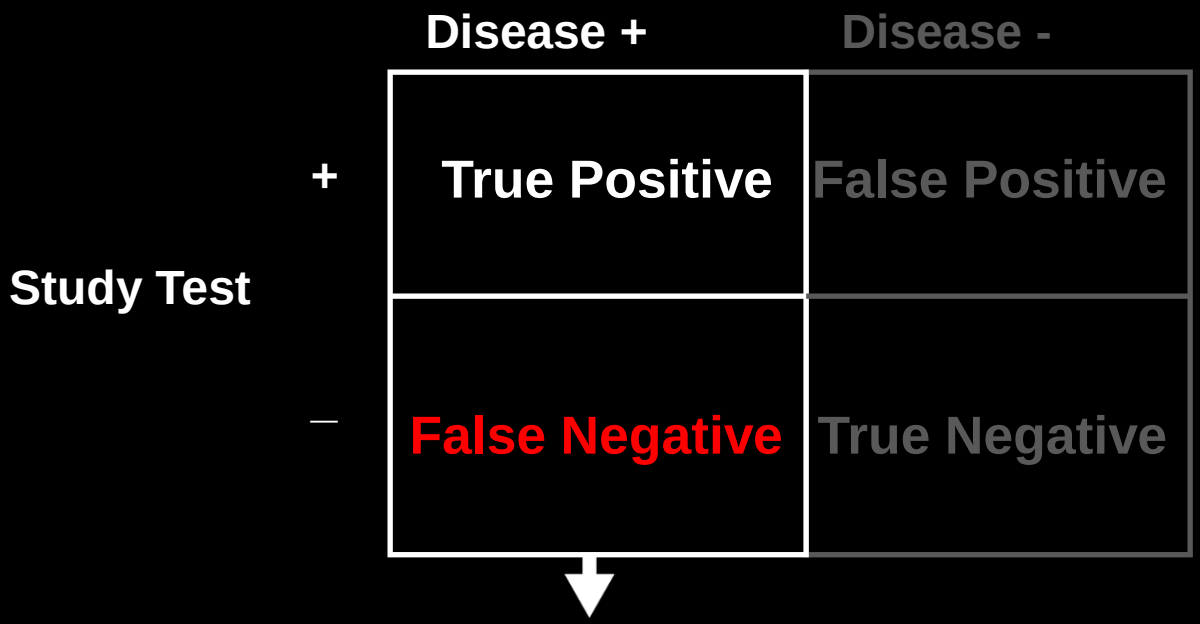
Two x Two (2 x 2) Table Notation

Study Test	"Gold Standard" Disease +	"Gold Standard" Disease -
+	True Positive	False Positive
–	False Negative	True Negative
	28%	72%

Another Visual



Sensitivity



Sensitivity = True positive rate or proportion of those with disease who test positive

$$= \frac{TP}{TP + FN}$$

Table —Comparison of the Results of Diagnostic Test (Ventilation-Perfusion Scan) With the Result of Reference Standard (Pulmonary Angiogram) Assuming Only High-Probability Scans Are Positive (Truly Abnormal)*

	Angiogram	
Scan Category	Pulmonary Embolus Present	Pulmonary Embolus Absent
High probability	102	14
Others	149	616
Total	251	630

Table –Comparison of the Results of Diagnostic Test (Ventilation-Perfusion Scan) With the Result of Reference Standard (Pulmonary Angiogram) Assuming Only High-Probability Scans Are Positive (Truly Abnormal)*

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Others	149	616
Total	251	630

$$\text{Sensitivity} = \frac{TP}{TP + FN} = \frac{102}{102 + 149} = \frac{102}{251} = 40\%$$

Specificity

Specificity = True negative rate or proportion of those without disease who test negative

$$= \frac{TN}{TN + FP}$$

Table –Comparison of the Results of Diagnostic Test (Ventilation-Perfusion Scan) With the Result of Reference Standard (Pulmonary Angiogram) Assuming Only High-Probability Scans Are Positive (Truly Abnormal)*

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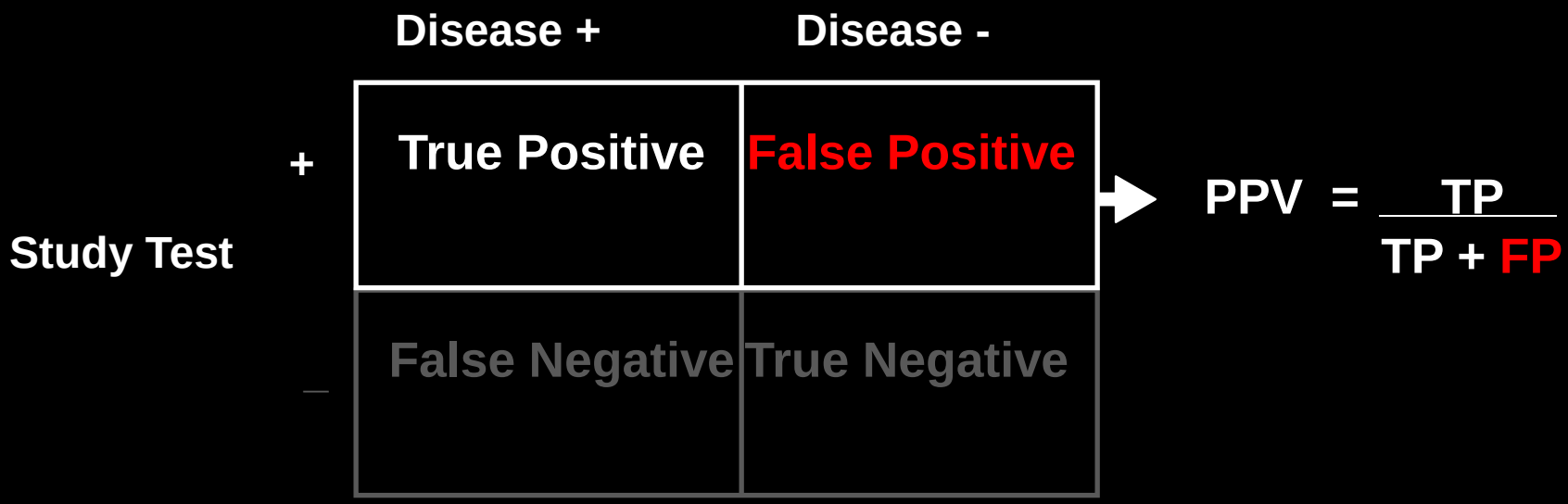
$$\text{Specificity} = \frac{TN}{TN + FP} = \frac{616}{616 + 14} = \frac{616}{630} = 98\%$$

False positive rate = 1 - specificity = 1.00 - 0.98 = 2%

Positive Predictive Value



- PPV = probability patient has disease if test is positive
- If there are 0 false positives, a test has a positive predictive value of 100%
- Increased specificity (lower false positive rate) increases PPV

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High probability	102	14
Others	149	616
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Positive Predictive Value = $\frac{TP}{TP + FP} = \frac{102}{102 + 14} = 88\%$

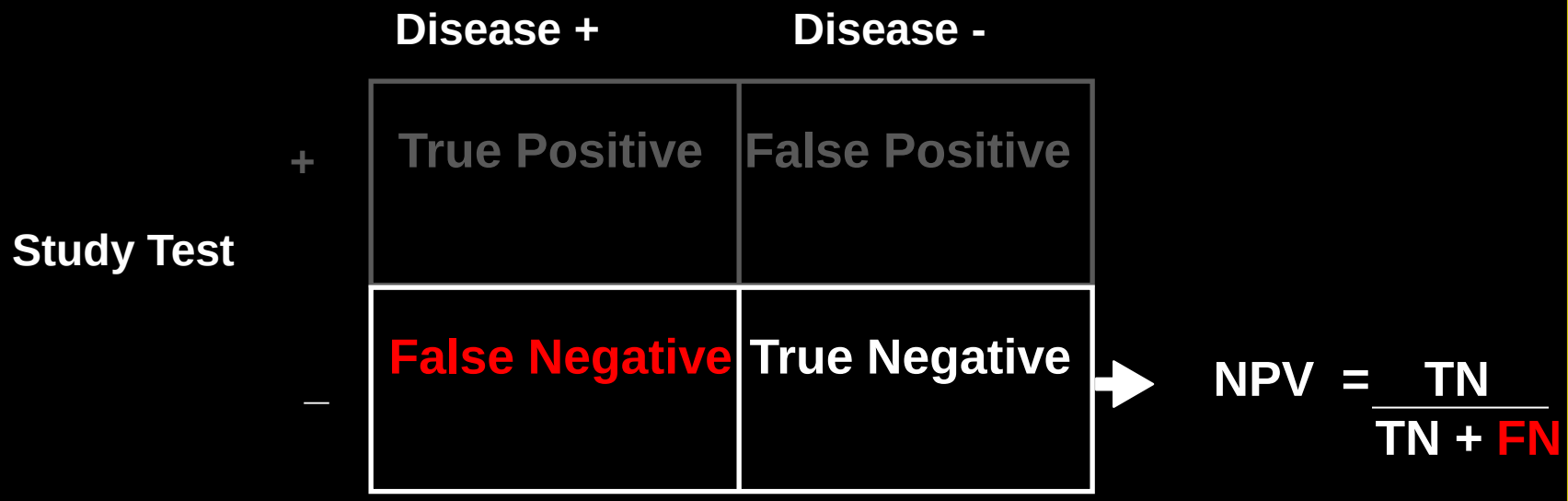
Increased specificity (low false positives) increases PPV

What Can We Conclude About High Probability V/Q Scan?

- Not very sensitive for PE
- If positive, has high PPV (because specificity is high)

→ What can we conclude about a normal V/Q Scan?

Negative Predictive Value



- NPV = probability patient does not have disease if test is negative
- If there are 0 false negatives, a test has a negative predictive value of 100%

Table —Comparison of the Results of Diagnostic Test (Ventilation-Perfusion Scan) With the Result of Reference Standard (Pulmonary Angiogram) Assuming Only Normal/Near-Normal Scans Are Negative (Truly Normal)*

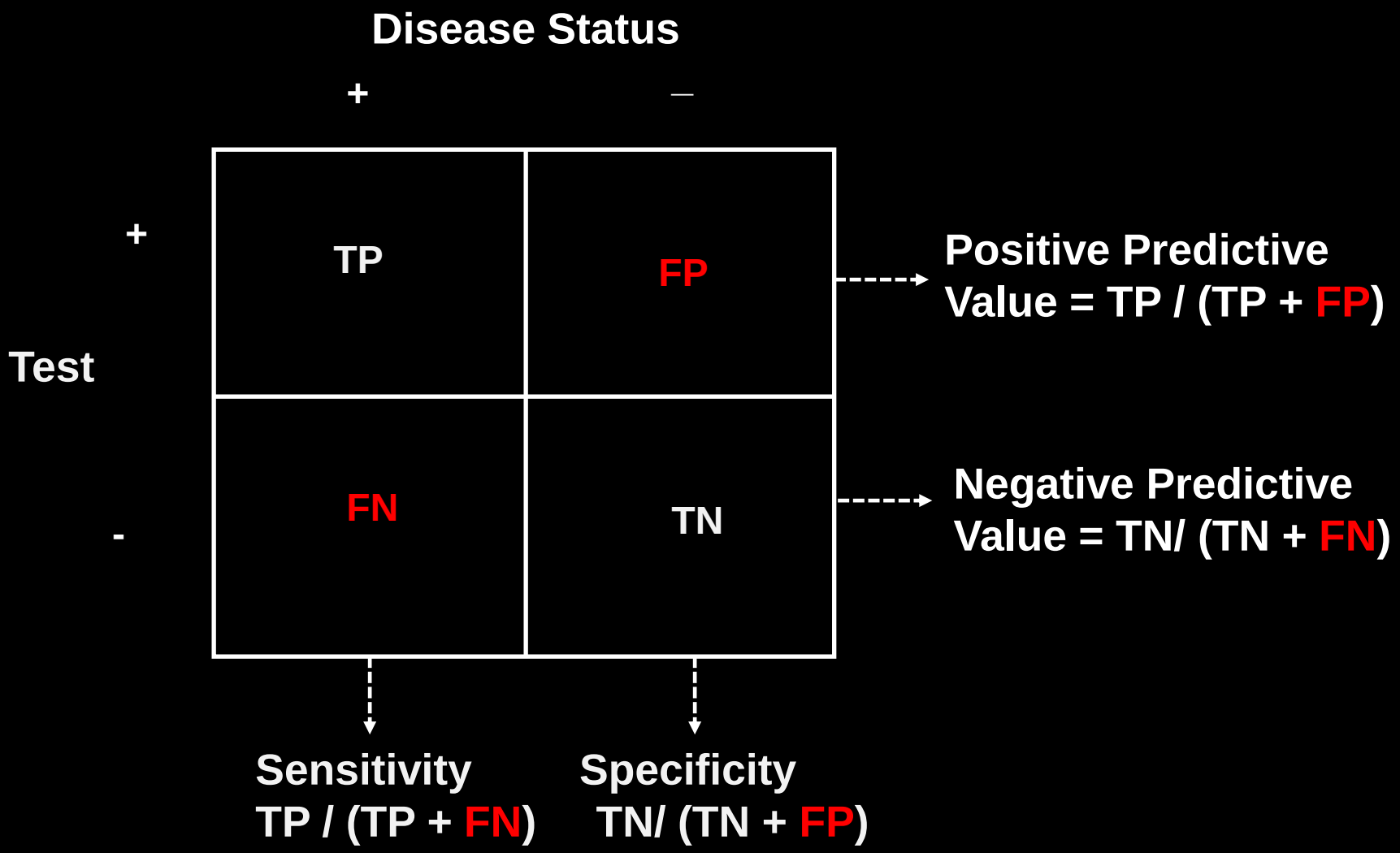
Scan Category	Angiogram: Pulmonary Embolus Present	Angiogram: Pulmonary Embolus Absent
High, intermediate, and low probability	246	504
Near normal/normal	5	126
Total	251	630

Table —Comparison of the Results of Diagnostic Test (Ventilation-Perfusion Scan) With the Result of Reference Standard (Pulmonary Angiogram) Assuming Only Normal/Near-Normal Scans Are Negative (Truly Normal)*

	Angiogram	
Scan Category	Pulmonary Embolus Present	Pulmonary Embolus Absent
High, intermediate, and low probability	246	504
Near normal/normal	5	126
Total	251	630

Negative Predictive Value $= \frac{TN}{TN + FN} = \frac{126}{126 + 5} = \frac{126}{131} = 96\%$

Increased sensitivity (low false negatives) increases NPV


Disease Status
+
–
+
Test
-
TP
FP
FN
TN
Positive Predictive Value = TP / (TP + FP)
Negative Predictive Value = TN/ (TN + FN)
Sensitivity TP / (TP + FN)
Specificity TN/ (TN + FP)

Examples

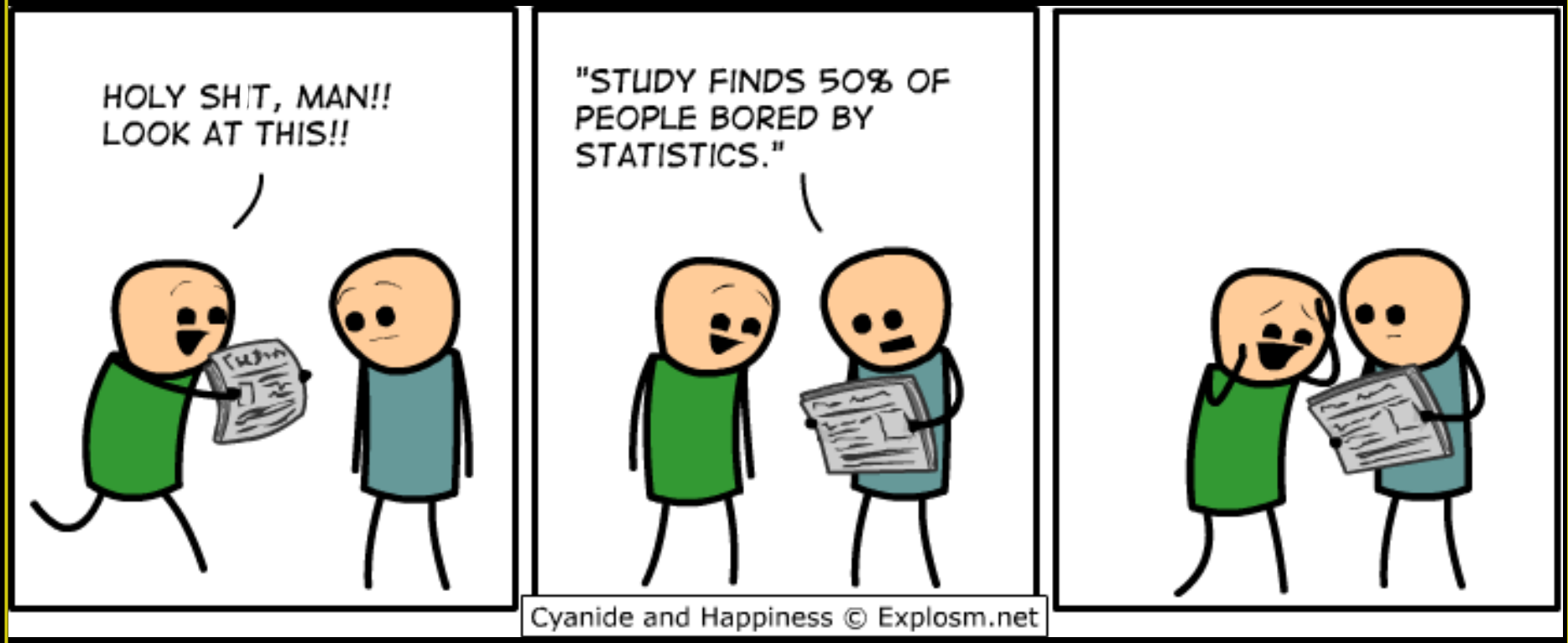
Disorder	Test	(Low False Positive) High PPV High Specificity	(Low False Negative) High NPV High Sensitivity
SLE	ds DNA	( )	( )
SLE	ANA	( )	( )

SPIN and **SNOUT**

Get positives right — Get Negatives right

Questions

- Elevator problem…



Outline

1. Clinical decision making and the role of a test

2. Two x two table notation – 4 test properties

3. **Likelihood ratios and calculation of post test probabilities**

4. Receiver operating characteristic curve (ROC)

5. Evaluating an article on a diagnostic test

Likelihood Ratio of a Positive Test

What are the odds that a positive test would be found in a person with the condition compared to a person without the condition?

$$LR(+) = \frac{\text{True positive rate}}{\text{False positive rate}} = \frac{\text{Sensitivity}}{\text{1 - Specificity}}$$

Table —Test Properties of Ventilation-Perfusion (V/Q) Scanning

V/Q Scan Result	Pulmonary Embolism: Present — No.	Pulmonary Embolism: Present — Proportion	Pulmonary Embolism: Absent — No.	Pulmonary Embolism: Absent — Proportion	Likelihood Ratio
High probability	102	102/251 = 0.406	14	14/630 = 0.022	18.3
Intermediate probability	105	105/251 = 0.418	217	217/630 = 0.344	1.2
Low probability	39	39/251 = 0.155	273	273/630 = 0.433	0.36
Normal/near normal	5	5/251 = 0.020	126	126/630 = 0.200	0.10
Total	251	...	630	...	...

Interpreting a Likelihood Ratio:

LR	Interpretation
>10	Strong evidence to rule in disease
5-10	Moderate evidence to rule in disease
2-5	Weak evidence to rule in disease
0.5-2	No significant change in likelihood of disease
0.2-0.5	Weak evidence to rule out disease
0.1-0.2	Moderate evidence to rule out disease
<0.1	Strong evidence to rule out disease

18.3 (95% CI: 10.7, 31.4)

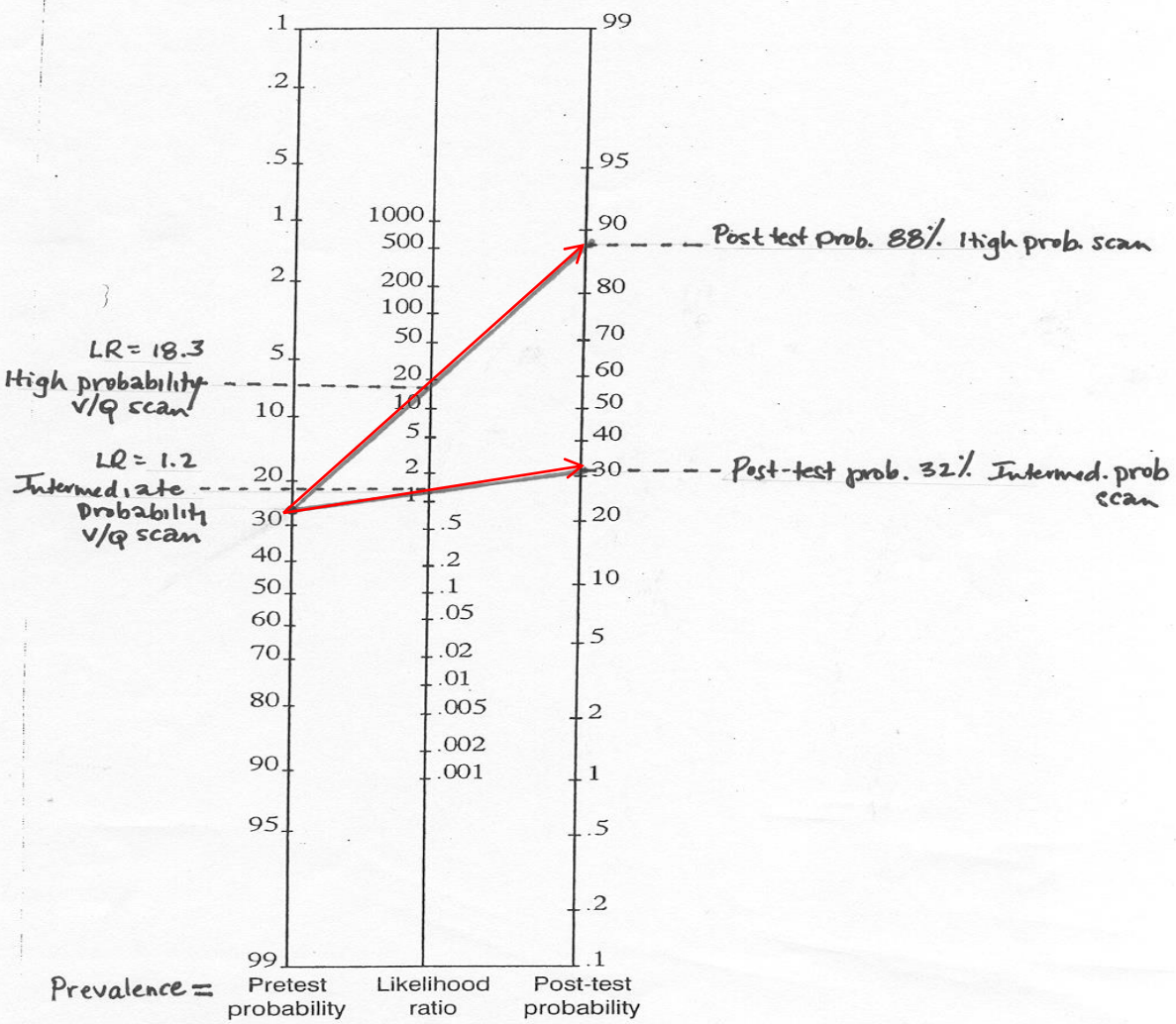


Figure A likelihood ratio nomogram. Adapted from Fagan T J 1975 Nomogram for Bayes's Theorem (c). New England Journal of Medicine 293: 257

Post-Test Probability = PPV

What is the probability of the condition given a positive test?

Can be answered in two equivalent ways:

1. **Post-test probability with LR times pre-test odds (Bayes' Simple Theorem)**

2. **Positive predictive value (PPV) using 2 x 2 table notation**

Likelihood Ratio of a Negative Test

What are the odds that a negative test would be found in a person with the condition compared to a person without the condition?

$$LR(-) = \frac{\text{False negative rate}}{\text{True negative rate}} = \frac{1 - \text{Sensitivity}}{\text{Specificity}}$$

Table —Test Properties of Ventilation-Perfusion (V/Q) Scanning

	Pulmonary Embolism				
	Present		Absent		
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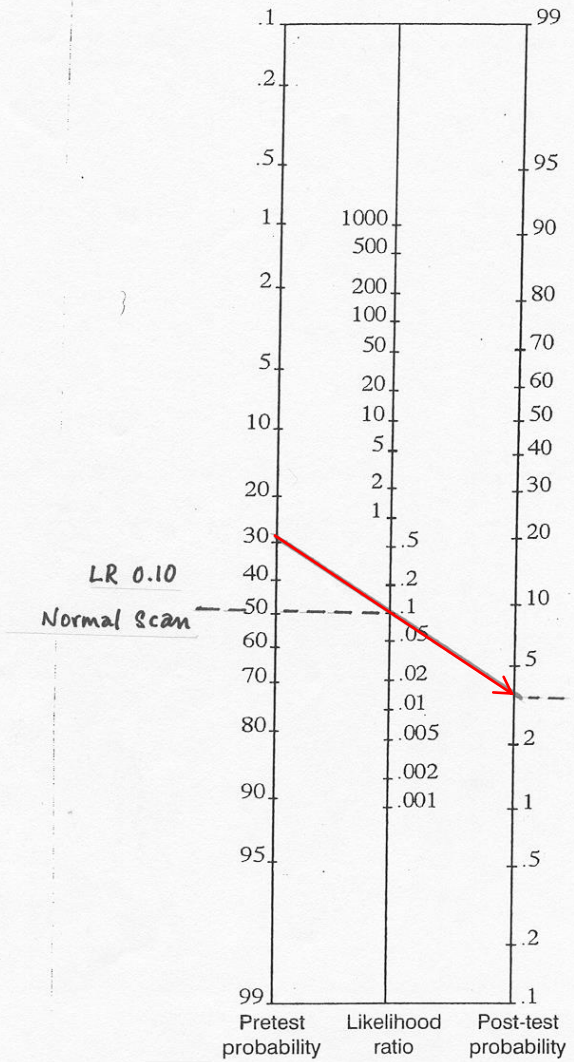
Nomogram for interpreting diagnostic test result



LR 0.10

Normal Scan

Post test Probability Normal Scan = 4%

OR

Negative Predictive Value = 96%

Figure A likelihood ratio nomogram. Adapted from Fagan T J 1975 Nomogram for Bayes's Theorem (c). New England Journal of Medicine 293: 257

Limitations of V/Q scan for diagnosis PE:

-High probability (116) or normal scan (131) = useful in 247 patients

-Intermediate (332) or low probability scan (312) = indeterminate in 634 patients

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	Pulmonary Embolism				
	Present		Absent		
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Total	251	...	630	...	...

Evaluation of Pulmonary Embolism

	High PPV	High NPV
V/Q Scan High probability	√	
V/Q Scan Normal		√
Pulmonary Angiogram	√	√
Spiral CT Scan	( )	( )
D-Dimer	( )	( )
Leg Vein Ultrasonogram	( )	( )

Measuring Diagnostic Procedures

Definitions

Sensitivity:	The proportion of subjects with a disease/condition who are positive by the test being studied. Sensitivity = (number of true positives by test)/(number with disease) x 100. Sensitivity determines how good a diagnostic test is for detecting the condition it is testing for and thus being positive in patients who actually have the condition. A test that is highly sensitive has a low false-negative rate. **SnNout: If a highly sensitive (Sn) test is negative (N), the disease is ruled out.**
Specificity:	The proportion of those without the disease/condition who are negative by the test being studied. Specificity = (number of true negatives by test)/(number without disease) x 100. Specificity determines how well the diagnostic test correctly identifies those patients who do not have the condition. A test that is highly specific has a low false-positive rate. **SpPin: If a highly specific (Sp) test is positive (P), the disease is ruled in.**
Positive Predictive Value:	The chance that an individual will have the characteristic of interest if the test for that characteristic is positive.
Negative Predictive Value:	The chance that an individual will not have the characteristic of interest if the test for that characteristic is negative.
Accuracy:	The total number of true positive and true negative values for a test, divided by the total number of tests.
Likelihood Ratio:	The likelihood ratio, a measure of the accuracy of a diagnostic test, determines the odds that the test result occurs in patients with the disease versus those without the disease. **The likelihood ratio for a positive test is the true-positive rate (sensitivity) divided by the false-positive rate (1 - specificity). The likelihood ratio for a negative test is the false-negative rate (1 - sensitivity) divided by true-negative rate (specificity).**

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Receiver Operating Characteristic (ROC) Curve

Extra:

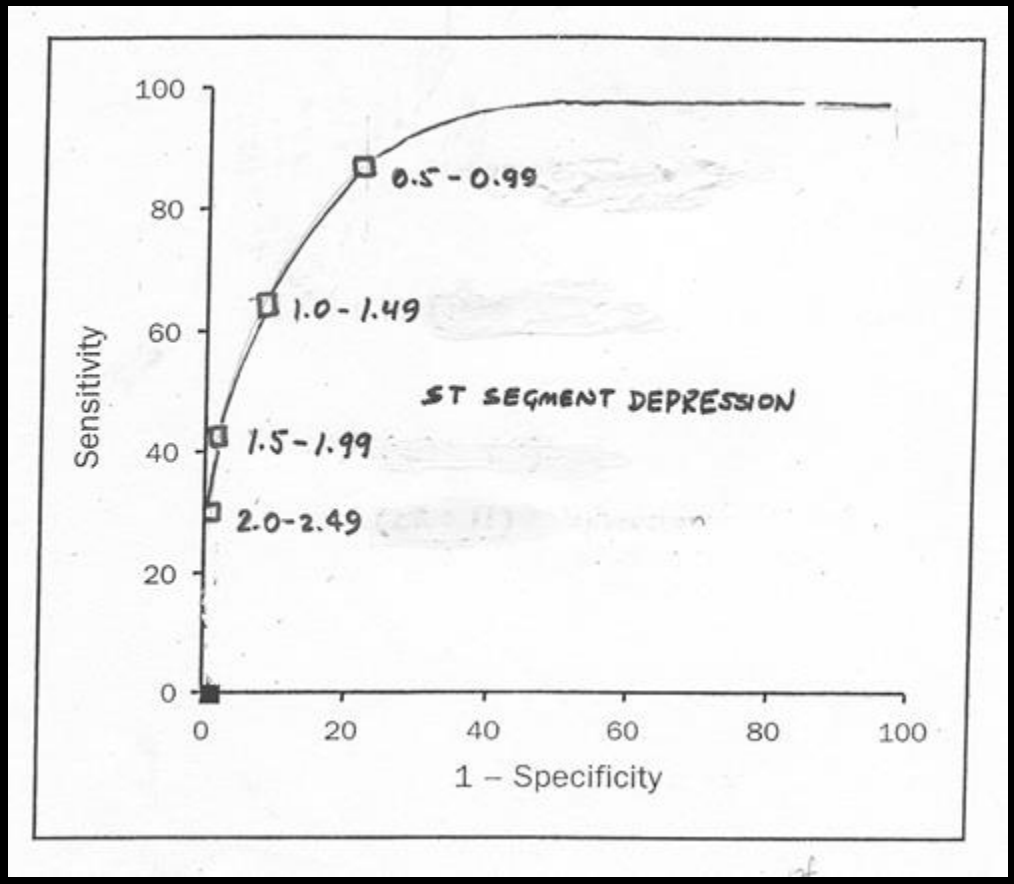
- **ROC Curve**
- **Area Under the Curve (AUC)**
- **C-Statistic (C: concordance)**
- **C-Index**
- **Discrimination**
- **Accuracy****

ROC Curve

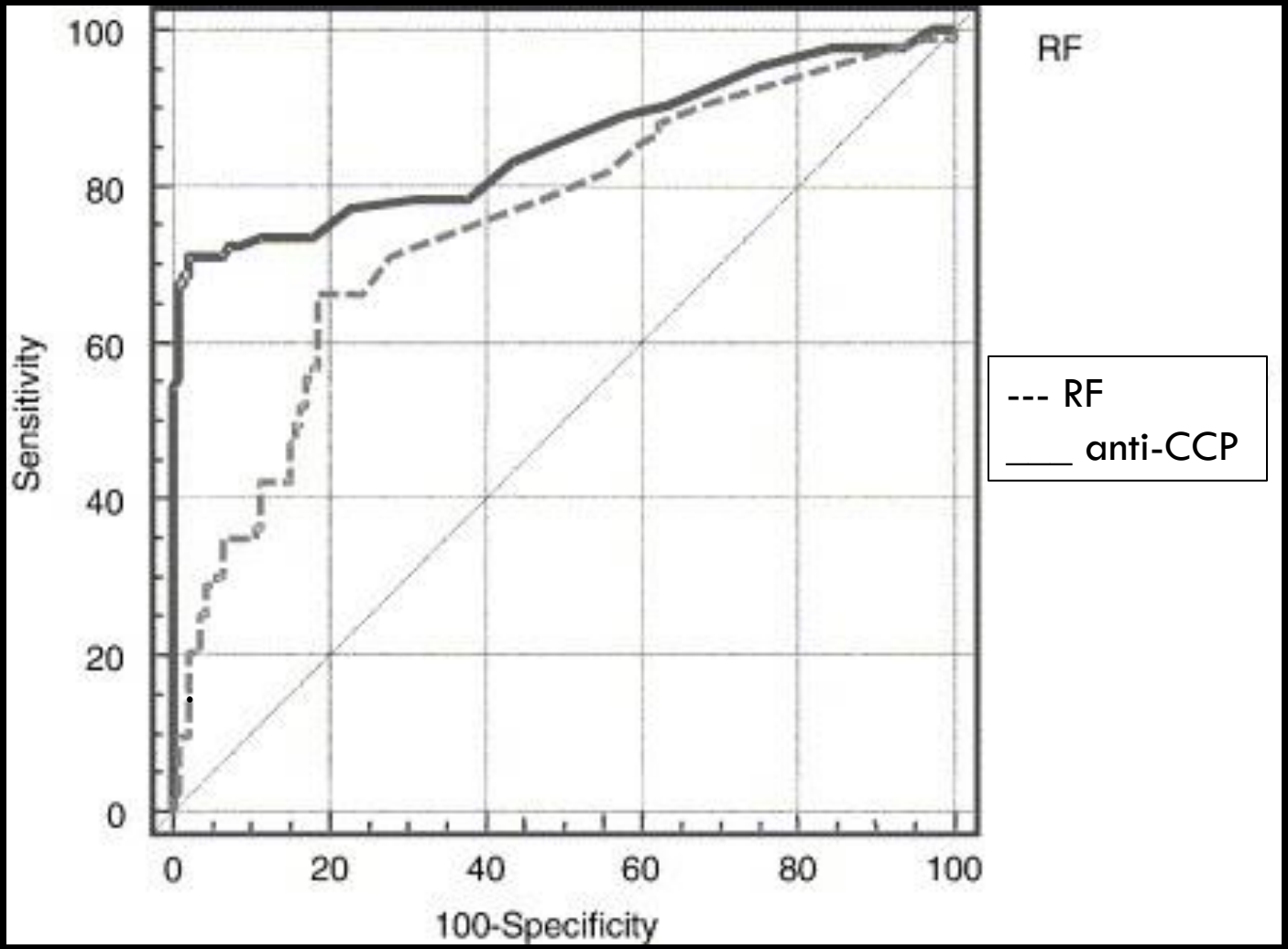
- Graph correlates true positives (sensitivity) and false positive rates (1 - specificity)
- Used in individual study when dealing with a diagnostic that is quantitative (continuous, e.g., blood pressures)
- Used when pooling a number of studies in a meta-analysis, validation studies, or sensitivity analyses
- Greater area under the curve, the more accurate the test
- Provides accuracy for any binary outcome

ROC Curve:

Exercise Electrocardiography for Angiographic Coronary Artery Disease

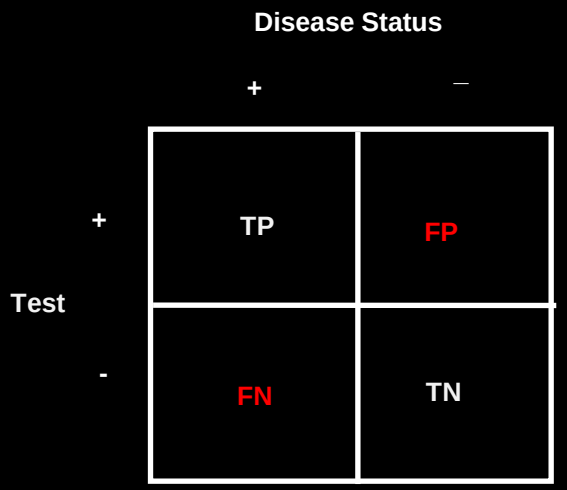


Which diagnostic test[2] – anti-CCP antibodies or RF– is more accurate in diagnosing rheumatoid arthritis?



If a test is 95% sensitive it would contain which of the following:

(A) 5% False positives
(B) 5% True positives
(C) 95% True positives
(D) 5% True negatives



A test with an 85% specificity means:

(A) 85% of patients with a positive test have the disease
(B) 15% of patients without the disease, falsely test positive
(C) 85% of patients without the disease test negative
(D) B & C are both correct

A test which is 100% accurate means that area under the ROC curve is 100%:

(A) True
(B) False

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Evaluating Diagnostic Test Article

1. Test compared with acceptable gold standard?
2. What is the prevalence of disease in study?
3. What are the statistical test properties in study?
4. Any potential sources of bias or variation?
5. Test still relevant and are more validations needed?

Sources of Bias and Variation[3]

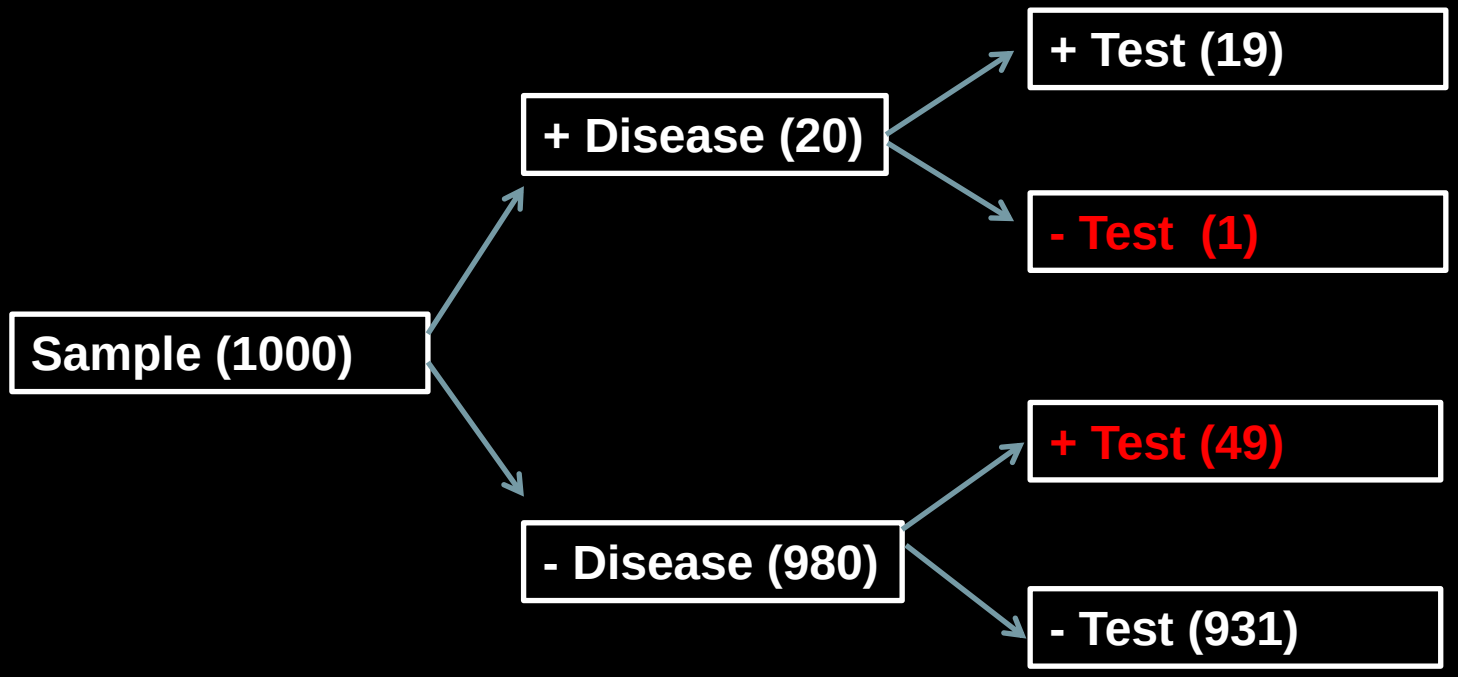
Population:	**Demographic features**
	Disease severity
	Disease prevalence
Test Protocol:	**Test technology variation**
Reference Standard:	**Partial verification bias**
Interpretation:	**Clinical review bias**
	Observer variability

***Confident about internal and external validity**

Importance of Prevalence (extra)

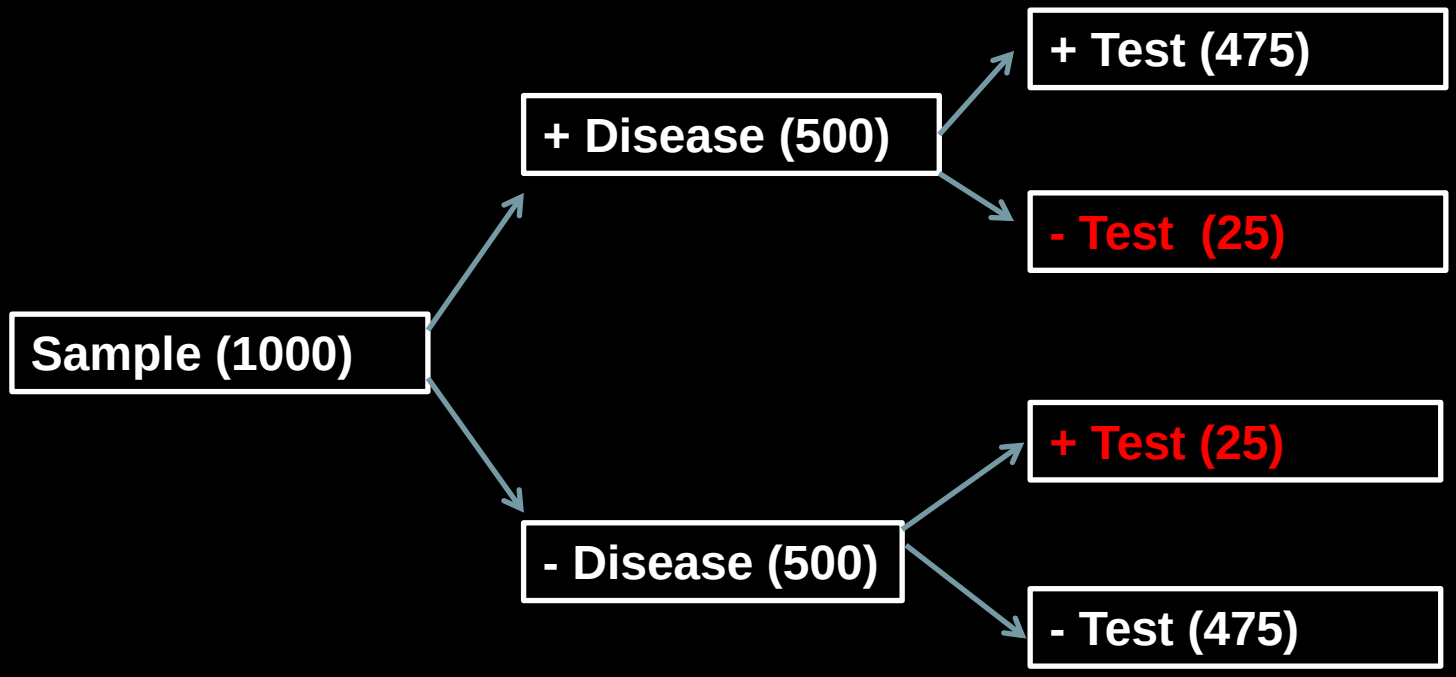
- Low or high prevalence affects test performance; i.e., more false positives and false negatives - influencing horizontal calculations.
- Result in extreme prevalence can result in wide confidence intervals
- Knowledge or awareness of prevalence of a disease in your clinical setting is important in application of test(s)
- Prevalence or pretest probabilities in 20-80% range can generate reasonable shifts in post-test probabilities

ART OF STATISTICS



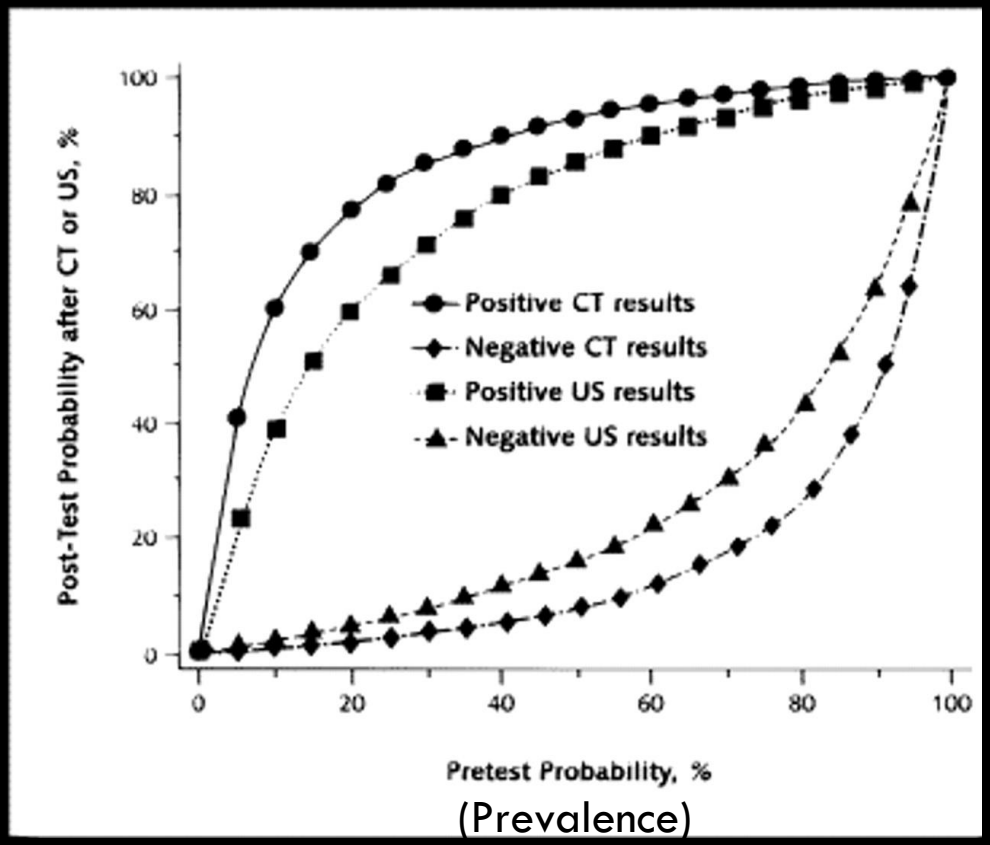
- Prevalence: 2%
- Sensitivity: 95%
- Specificity: 95%
- Probability of disease given positive test: 19/(19+49) = 28%

ART OF STATISTICS



- Prevalence: 50%
- Sensitivity: 95%
- Specificity: 95%
- Probability of disease given positive test: 475/(475+25) = 95%

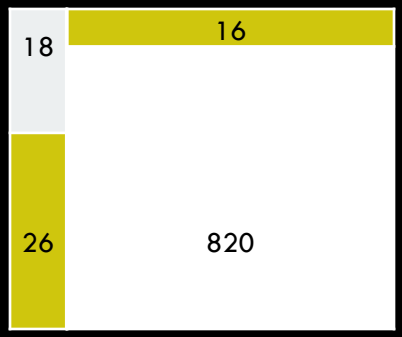
Knowledge Gained[4]



- **Example: CT and US to detect acute appendicitis in adults and adolescents.**

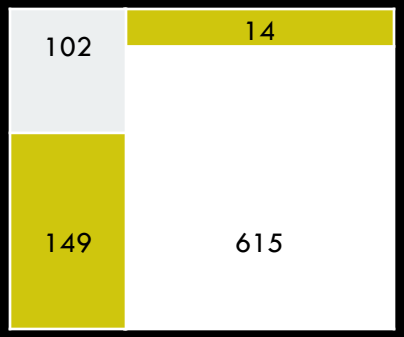
What is the probability of the condition given a positive test? (extra)

General Medicine Clinic



Pre-test Probability: 5%
Post-Test Probability: 53%

Specialist Clinic



Pre-test Probability: 29 %
Post-Test Probability: 88%

Limitations of EBM

- Studies looks within specific context - need to take into account the variation between your patients and study sample
- Estimating and knowing pre-test probability takes practice, experience, and investigation

Key Points

- Actual Probability = prevalence = pretest probability
- Multiple statistical test properties can be confusing
- Limitations of EBM

Identifying depression in primary care: a comparison of different methods in a prospective cohort study

Verena Henkel, Roland Mergl, Ralf Kohnen, Wolfgang Maier, Hans-Jürgen Möller, Ulrich Hegerl

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Depressive disorders are a major health problem in primary care, and at least half of these disorders remain undetected.[1] There are two recommended approaches to diagnosing depression in primary care: one is to perform routine screening, and the other is to evaluate patients only when the clinical presentation triggers the suspicion of depression. Our aim was to compare these two approaches, and to compare three different screening tools in order to evaluate which would be most appropriate for use in primary care. From among the many available screening tools, we selected three brief, self rating instruments: one disorder-specific (the depression module of the brief patient health questionnaire (B-PHQ, 9 items)),[2] one broad based (the general health questionnaire (GHQ-12, 12 items)),[3] and one that is less restricted to both issues (WHO-5 wellbeing index (WHO-5, 5 items)).[4]

Methods and results

Eighteen primary care facilities participated in our prospective cohort study. The study protocol was approved by our local ethics committee. On one given day, all patients who presented in one of the practices were asked to complete the three screening questionnaires before seeing a doctor. The doctors who treated the patients remained blind to the questionnaire results until they had completed a brief "physician's encounter form" to indicate their clinical assessment of their patient's current diagnoses.

Within a period not exceeding six days after they had completed the questionnaires, the patients were contacted by telephone for a fully structured, standardised psychiatric interview (composite international diagnostic interview (CIDI)) conducted by a trained psychologist blind to the screening results. We chose the composite international diagnostic interview as the reference standard because its reliability and validity have been established.[5] The interviewing psychologists met a high standard of inter-rater reliability.

The main outcome measures were, firstly, the family doctors' performance in detecting depression without any tool to help guide diagnosis decisions and, secondly, the test accuracy of the screening questionnaires. We calculated sensitivity, specificity, and predictive values using two-by-two tables. We used two statistical tests to compare differences of characteristics of test accuracy (table).

For 431 patients, all screening questionnaires, the composite international diagnostic interview, and the physician's encounter form were completed. Of these patients, 17% suffered from any depressive disorder and 83% did not.

Comment

The sensitivity of the family doctors' unaided clinical diagnoses was 65%. With standard cut-off points, the briefest screening questionnaire (and therefore the most practical to use), the WHO-5, produced significantly greater sensitivity (93%) and a better negative predictive value (98%) than the other questionnaires (see table). However, the brief patient health questionnaire and unaided clinical diagnosis produced better specificity. The brief patient health questionnaire also produced the best positive predictive value. However, since screening tools are designed to identify all patients at risk for a disorder, sensitivity and negative predictive value are the most important operating characteristics.

Comparison of test accuracy of screening questionnaires for depression and family doctors' unaided clinical diagnosis. Values are means (95% confidence intervals) unless stated otherwise

Measures of test accuracy	Screening questionnaires			Unaided clinical diagnosis (UCD)	Significant differences (P≤0.05, one sided tests)§
	WHO-5*	GHQ-12†	B-PHQ‡		
Sensitivity (%)	93 (85 to 98)	85 (74 to 92)	78 (66 to 87)	65 (53 to 76)	WHO-5>GHQ-12, B-PHQ>UCD
Negative predictive value (%)	98 (95 to 99)	95 (92 to 98)	95 (92 to 97)	91 (88 to 94)	WHO-5>B-PHQ>UCD, GHQ-12>UCD
Specificity (%)	64 (59 to 69)	62 (57 to 67)	85 (81 to 89)	74 (69 to 79)	B-PHQ>UCD>WHO-5, UCD>GHQ-12
Positive predictive value (%)	34 (28 to 41)	31 (25 to 38)	51 (42 to 61)	34 (26 to 42)	B-PHQ>WHO-5>GHQ-12, B-PHQ>UCD

*WHO-5 wellbeing index (scoring procedure as indicated in *World Health Organization info package*[4]).
†General health questionnaire (scoring procedure as indicated in Goldberg 1978[3]).
‡Brief patient health questionnaire (scoring procedure as indicated in Spitzer et al 1999[2]).
§McNemar's test to compare sensitivities and specificities, analogue of McNemar's test to compare predictive values.

Our results suggest that the use of WHO-5 could improve family doctors' ability to detect depression, supporting the World Health Organization's recommendation that every patient in primary care should participate in a screening process with the completion of WHO-5 as a standard first step, done in the waiting room.[4] The questionnaire can easily be scored by hand. Patients who score positively for depression should be examined by their doctor in order to confirm a diagnosis of depression or to rule out normal distress or physical causes of depression. At this stage, doctors could use the brief patient health questionnaire as a checklist.

We hope that our results favouring such a simple, two stage screening process for depression in primary care, starting with the questionnaire WHO-5, will encourage further research in other countries.

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Contributors: VH had the idea for this paper and drafted the paper. RM analysed the data. RK, WM, H-JM, and UH commented on the study protocol and the text of the paper. UH is the speaker of the "German Research Network on Depression." VH and UH are guarantors for the study.

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Competing interests: None declared.

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Questions

1. Gold standard?

2. Prevalence?

3. Best screening questionnaire, why?

4. Limitations/Bias?

5. Applicable to your patients?

- Final Example

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Extra Information: ???????
Post-Test Probability using Bayes

Probability of condition given a positive test:

Bayes' Theorem: $P(A \mid B) = \dfrac{P(A)\,P(B \mid A)}{P(B)}$

? Or $P(A \cap B) / P(B)$

Example:

$P(A)$ = probability of PE, prevalence 0.28

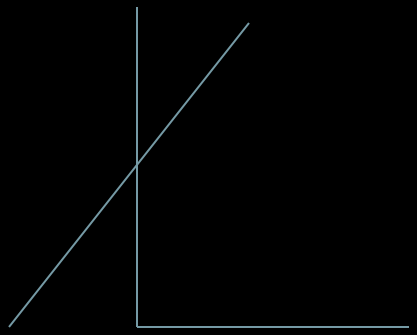
$P(B \mid A)$ = probability of patient with PE getting a 'High' classification, sensitivity 0.40

$P(B)$ = probability of a "High" classification, 0.13

$$\frac{(0.28)\,(0.40)}{(0.13)} = 0.86$$, *some rounding error included*

- Would the closes ratio of sen/spec to 1 = the best cut-off? Yes, this is like the X style graph to find the best cut-off (plotting sen vs. spec)

- Optimal cutoff, provides maximized intercept on y axis.



- SPIN and SNOUT

- Serial testing, Clinical Epidemiology page 56

  Post-test probability = new pretest probability

  Next, new post-test probability = new pretest * LR

Serial Tests: http://www.talkstats.com/showthread.php/61723-Help-with-Bayesian-question-please/page2

- Pretest Probability (i.e., population prevalence): 0.0001

  Pretest Odds: 0.0001 / (1 - 0.0001) or 0.0001

  +LR (i.e., SEN/(1-SPEC)): 0.90 / (1 - 0.98) or 45

  Post-Test#1 Odds also New Pre-Test#2 Odds: 0.0001 * 45 or 0.0045

  New Pre-Test#2 Probability (not used): 0.0045 / 1 + 0.0045 or 0.0045

  New Post-Test#2 Odds: 0.0045 * 45 = 0.2025

  New Post-Test#2 Probability: 0.2025 / 1 + 0.2025 or 0.168

- Serial Tests Pre-test probability * +LR1 * +LR2 * +LRk; k= number of tests

Bayes Theorem

Likelihood
Probability of collecting this data when our hypothesis is true

Prior
The probability of the hypothesis being true before collecting data

$$P(H|D) = \frac{P(D|H)\,P(H)}{P(D)}$$

Posterior
The probability of our hypothesis being true given the data collected

Marginal
What is the probability of collecting this data under all possible hypotheses?