SCREENING AND DIAGNOSTIC TEST Modality for EBM

Epidemiology and Biostatistics
2012
**KEY REFERENCES**


Coggon D, Rose J, Barker DJ P. Epidemiology for the uninitiated. Available from http://resources.bmj.com/bmj/readers/readers/epidemiology-for-the-uninitiated/10-screening


Glaziou, P. Centre of Evidence Based Medicine, Oxford.
Specific Learning Objectives

1. Explain the definition, characteristics, purpose and use of screening test.
2. Explain the role of screening test in clinical decision making.
3. Explain the definition of diagnostic study and their role in Evidence Based Practice.
SCREENING: DEFINITION

“The PRESUMPTIVE identification of UNRECOGNIZED disease or defect by the application of tests, exams or other procedures which can be applied RAPIDLY to sort out apparently well persons who PROBABLY have a disease from those who PROBABLY do not”*

Key Elements:

Disease or defect - test/procedure – probability - population

*Commission on Chronic Illness, 195
Why screening? 3 characteristics

1. Disease/disorder is an important public health problem
   High prevalence - Serious outcome – High cost for care

2. Early Detection in asymptomatic (pre-clinical) individuals is possible

3. Early detection and treatment can affect the course of disease
   (or affect the public health program)
What to test: is it always obvious?
’VARIABILITY IS THE LAW OF LIFE’

NO TWO FACES ARE THE SAME, NO TWO BODIES ARE ALIKE.

NO TWO INDIVIDUALS REACT OR BEHAVE ALIKE UNDER THE ABNORMAL CONDITIONS
GLAUCOMA: DEFINITIONS?

OPTIC NERVE DAMAGE
INCREASED PRESSURE BLOCKAGE

AT WHAT PRESSURE DOES IT START TO BE SYMPTOMATIC?

http://www.bmj.com/content/328/7431/97.full
THE RATE AT WHICH RAISED INTRAOCULAR PRESSURE CAUSES OPTIC NERVE DAMAGE DEPENDS ON MANY FACTORS, INCLUDING THE PRESSURE AND WHETHER GLAUCOMATOUS DAMAGE IS EARLY OR ADVANCED.

IN GENERAL, PRESSURES OF 20-30 MM HG USUALLY CAUSE DAMAGE OVER SEVERAL YEARS, BUT PRESSURES OF 40-50 MM HG CAN CAUSE RAPID VISUAL LOSS AND ALSO PRECIPITATE RETINOVASCULAR OCCLUSION.

http://www.bmj.com/content/328/7431/97.full
Ms Eto’o, blurred vision

Potential problems at:

Cornea, lens, aquos vitreus, optic nerve

What screening test would you choose?

- anamnesis
- Visual inspection
- Tonometry

Gold standard ???

What screening test would you choose?
Healthy eyes
Glaucmatous eyes
Healthy eyes
Glaucomatous eyes

NUMBER OF EYES

INTRAOCULAR PRESSURE IN MM HG
THE CRITICAL POINT
AT WHICH ONE CONSIDERS
THE TEST INTERPRETATION
TO CHANGE
FROM NEGATIVE TO POSITIVE
(OR FROM ONE STAGE TO ANOTHER)
CHANGING THE CUT-OFF POINTS

TOO LOW:
GREATER # SELECTED, BUT COULD ALSO MEAN UNNECESSARY ANXIETY (AND COST) FOR FALSE POSITIVE.

TOO HIGH:
SMALLER # SELECTED, BUT COULD ALSO MEAN LEAVING OUT WITH TRUE RISK OF DEVELOPING BLINDNESS.
Where do we set the cut-off for a screening test?

Consider:

- The impact of high number of false positives: anxiety, cost of further testing

- Importance of not missing a case: seriousness of disease, likelihood of re-screening
WHAT TEST(S) ARE AVAILABLE FOR ONE PARTICULAR DISEASE FIT FOR SCREENING PURPOSE AT ONE PARTICULAR MEDICAL FACILITY ARE AFFORDABLE (BY THE PATIENTS) ARE ACCEPTABLE (FOR THE PATIENTS)
A BOY, 6 years, chronic cough, night sweat.

Differential diagnosis are: ....

For each stage of cdm in diagnosis:
- What screening test would you choose?
- Is there a gold standard test?
CLINICAL DECISION MAKING

SCIENTIFICALLY - SOUND SELECTION PROCESS OF: MODALITIES IN DIAGNOSIS/THERAPEUTIC TO CHANGE PROBABILITY OF MORBID CONDITION/ CURE
APPARENTLY WELL POPULATION
(Well persons plus those with undiagnosed disease)

Population To Be Tested

Negatives
(Persons presumed to be free of disease under study)

• Negatives on test

⊗ Positives on test, no disease

• Positives on test, disease present

Positives
(Persons presumed to have the disease or be at increased risk in future)

Disease or Risk Factor Present

Disease or Risk Factor Absent
Evaluation Criteria of a Test

Modality

• Validity:
  provide a good indication of who does and does not have disease
  - Sensitivity of the test
  - Specificity of the test

• Reliability (precision):
  gives consistent results when given to similar persons under the same conditions, or performed by different observers

• Yield:
  Amount of disease detected in the population, relative to the effort
  - Positive predictive value
Validity of Screening Test (Accuracy)

- Sensitivity:
  How much is the test detecting true cases of disease?
  (Ideal is 100%: 100% of cases are detected)

- Specificity:
  How much is the test excluding those without disease?
<table>
<thead>
<tr>
<th>True Cases of Glaucoma</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP &gt; 22: Yes</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>1900</td>
</tr>
<tr>
<td>(total)</td>
<td>100</td>
<td>2000</td>
</tr>
</tbody>
</table>

Sensitivity = 50% (50/100)  False
Negative = ??
Specificity = 95% (1900/2000) False Positive
Reliability (reproducibility)

Agreement within and between examiners

Inter-Observer Agreement in Grading Severity of Cataract Grade

<table>
<thead>
<tr>
<th>Examiner 2</th>
<th>&lt;1</th>
<th>1-&lt;2</th>
<th>2-&lt;3</th>
<th>3-&lt;4</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>10</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1-&lt;2</td>
<td>1</td>
<td>20</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2-&lt;3</td>
<td>0</td>
<td>1</td>
<td>20</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3-&lt;4</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

% Agreement = 81.3% ; Kappa = 0.76
Validity versus Reliability of Screening Test

Examiner 1  Examiner 2  Examiner 3

Good Reliability

True cases

Low Validity
Principles for Screening Programs

1. Condition should be an important health problem
2. There should be a recognizable early or latent stage
3. There should be an accepted treatment for persons with condition
4. The screening test is valid, reliable, with acceptable yield
5. The test should be acceptable to the population to be screened
6. The cost of screening and case finding should be economically balanced in relation to medical care as a
UNDERSTANDING DIAGNOSTIC TEST
METHOD 1: NATURAL FREQUENCIES GRID

| Person without the disease | ○ |
| Person with the disease    | ● |

Assume that the prevalence of the disease is 4%
This is also called Pre-test probability
Assume that of the 4 people with the disease, 3 are picked up by the test

<table>
<thead>
<tr>
<th>Person without the disease</th>
<th>⬜️</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person with the disease</td>
<td>⬜</td>
</tr>
<tr>
<td>Person who tests positive</td>
<td>🔴</td>
</tr>
<tr>
<td>Person who tests negative</td>
<td>🔵</td>
</tr>
</tbody>
</table>
Assume that of the test is positive for a further 7 people who don’t have the disease

<table>
<thead>
<tr>
<th>Person without the disease</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Person with the disease</td>
<td></td>
</tr>
<tr>
<td>Person who tests positive</td>
<td></td>
</tr>
<tr>
<td>Person who tests negative</td>
<td></td>
</tr>
<tr>
<td>True positive on the test</td>
<td></td>
</tr>
<tr>
<td>False positive on the test</td>
<td></td>
</tr>
</tbody>
</table>

![Diagram showing the distribution of test results]

- **True positive on the test**: The person actually has the disease and tests positive.
- **False positive on the test**: The person does not have the disease but tests positive.
- **True negative on the test**: The person does not have the disease and tests negative.
- **False negative on the test**: The person actually has the disease but tests negative.
The remainder of the sample are negative on the test

<table>
<thead>
<tr>
<th>Person without the disease</th>
<th>〇</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person with the disease</td>
<td>●</td>
</tr>
<tr>
<td>Person who tests positive</td>
<td>〇</td>
</tr>
<tr>
<td>Person who tests negative</td>
<td>〇</td>
</tr>
<tr>
<td>True positive on the test</td>
<td>〇</td>
</tr>
<tr>
<td>False positive on the test</td>
<td>〇</td>
</tr>
<tr>
<td>True negative on the test</td>
<td>〇</td>
</tr>
<tr>
<td>False negative on the test</td>
<td>〇</td>
</tr>
</tbody>
</table>
### Sensitivity

<table>
<thead>
<tr>
<th>Person without the disease</th>
<th>Person with the disease</th>
<th>Person who tests positive</th>
<th>Person who tests negative</th>
<th>True positive on the test</th>
<th>False positive on the test</th>
<th>True negative on the test</th>
<th>False negative on the test</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☰</td>
<td>☰</td>
<td>☰</td>
<td>☳</td>
<td>☰</td>
<td>☰</td>
<td>☰</td>
</tr>
</tbody>
</table>

- **Sensitivity** is the proportion of people with the disease correctly identified by the test.
- In this case is $\frac{3}{4} = 75\%$.
SPECIFICITY

- SPECIFICITY is the proportion of people without the disease correctly identified by the test.
- In this case, specificity is \((96-7)/96\) or 93%.
If someone is positive on the test, what are the chances that he/she has the disease?

<table>
<thead>
<tr>
<th>Person without the disease</th>
</tr>
</thead>
</table>
| Person with the disease   | ![Image](image.png)  
| Person who tests positive | ![Image](image.png)  
| Person who tests negative | ![Image](image.png)  
| True positive on the test | ![Image](image.png)  
| False positive on the test | ![Image](image.png)  
| True negative on the test | ![Image](image.png)  
| False negative on the test | ![Image](image.png)  

- Probability = $\frac{3}{10} = 30\%$
- This is the POSITIVE PREDICTIVE VALUE (the value of the test in predicting a positive result)
If someone is negative on the test, what are the chances that he/she does not have the disease?

- **Probability** = 89/90 = 99%
- This is the **NEGATIVE PREDICTIVE VALUE** (the value of the test in predicting a negative result)
SENSITIVITY, SPECIFICITY AND PREDICTIVE VALUES

• For sensitivity and specificity, the reference variable (‘denominator’) is the DISEASE

• For predictive value, the reference variable (‘denominator’) is the TEST
## METHOD 2: NATURAL FREQUENCIES TREE

<table>
<thead>
<tr>
<th>Population</th>
<th>100</th>
</tr>
</thead>
</table>


In every 100 people, 4 will have the disease.

Population

<table>
<thead>
<tr>
<th>Disease +</th>
<th>Disease -</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>96</td>
</tr>
</tbody>
</table>

If these 100 people are representative of the population at risk AND there are 4 cases within the population. What can you tell based on the data available?

Pre-test probability of having the disease

Disease prevalence
OF THE 4 PEOPLE WITH THE DISEASE, THE TEST DETECTS ONLY 3

Population

<table>
<thead>
<tr>
<th>Disease +</th>
<th>Disease -</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>96</td>
</tr>
</tbody>
</table>

Test +

<table>
<thead>
<tr>
<th>Test +</th>
<th>Test -</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

In other words, the ........... is ...... %
AMONG THE 96 PEOPLE WITHOUT THE DISEASE, THERE ARE 7 WHOSE TESTS ARE POSITIVE. THE CORRECTLY DETECTED RATE OF HEALTHY PEOPLE IS $\frac{3}{89}$.

In other words, the ..........is ..........%
AMONG THOSE WHOSE TESTS ARE POSITIVE, 3 IN 10 ACTUALLY HAVE THE DISEASE

<table>
<thead>
<tr>
<th>Population 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease + 4</td>
</tr>
<tr>
<td>Disease - 96</td>
</tr>
<tr>
<td>Test + 3</td>
</tr>
<tr>
<td>Test + 7</td>
</tr>
<tr>
<td>Test - 1</td>
</tr>
<tr>
<td>Test - 89</td>
</tr>
</tbody>
</table>

This is also called as

The .................

........is ..........%
AMONG THOSE WHOSE TEST ARE NEGATIVE, 89 OF 90 DO NOT HAVE THE DISEASE

<table>
<thead>
<tr>
<th>Population</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease +</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease -</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>96</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test +</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test +</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test -</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test -</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>89</td>
<td></td>
</tr>
</tbody>
</table>

The ...........is ............%.
PREDICTIVE VALUES AND CHANGING PREVALENCE, SUPPOSE THE 4 CASES IS PUT IN A LARGER POPULATION OF 1000 PEOPLE, other are healthy (PREVIOUSLY 100 PEOPLE)

What changes do you see? The magnitude of the changes is from ..... % to ..........%
CHANGING PREVALENCE:
WHICH VALUE(S) CHANGE??

Population
1000

Disease +
4

Test +
3

Test -
1

Disease -
996

Test +
70

Test -
926

What happens to Sensitivity and Specificity?
HOW IS POSITIVE PREDICTIVE VALUE AT THIS PREVALENCE?

What changes do you see?

Population
1000

Disease +
4

Test +
3

Disease -
996

Test +
70

Test -
1

The ............. Is Now ...... %
Previously .... %

Test -
926
HOW IS NEGATIVE PREDICTIVE VALUE AT THIS PREVALENCE

What changes do you see? How big is the change?

Population
1000

Disease +
4

Disease -
996

Test +
3

Test +
70

Test -
1

Test -
926

The .......... is .......... %.
NOTES in LOW PREVALENCE EVENTS

• Even highly specific tests, may yield a high number of false positive results

• Because of this, under such circumstances, the Positive Predictive Value of a test is low

• However, this has much less influence on the Negative Predictive Value

→ state when to apply the test of this modality in screening process !!
RELATIONSHIP BETWEEN PREVALENCE AND PREDICTIVE VALUE

Based on a test with 90% sensitivity and 82% specificity

Difference between PPV and NPV relatively small

Difference between PPV and NPV relatively large
RELATIONSHIP BETWEEN PREVALENCE AND PREDICTIVE VALUE

Based on a test with 75% sensitivity and 93% specificity
PERFORMANCE OF A TEST WITH CHANGING PREVALENCE

A: Sensitivity = 0.9
Specificity = 0.9
LR+ = 9.0

B: Sensitivity = 0.7
Specificity = 0.7
LR+ = 3.0

C: Sensitivity = 0.5
Specificity = 0.5
LR+ = 1.0
The likelihood that someone with the disease will have a positive test is $\frac{3}{4}$ or 75%. This is the same as the sensitivity.
The likelihood that someone without the disease will have a positive test is $\frac{7}{96}$ or 7%. This is the same as the (1-specificity)
LIKELIHOOD RATIO

\[
\text{LIKELIHOOD RATIO} = \frac{\text{LIKELIHOOD OF POSITIVE TEST GIVEN THE DISEASE}}{\text{LIKELIHOOD OF POSITIVE TEST IN THE ABSENCE OF THE DISEASE}}
\]

\[
= \frac{\text{SENSITIVITY}}{1 - \text{SPECIFICITY}} = \frac{0.75}{0.07} = 10.7
\]

A Likelihood Ratio of 1.0 indicates an uninformative test (occurs when sensitivity and specificity are both 50%)

The higher the Likelihood Ratio, the better the test (other factors being equal)
### Method 3: ‘Traditional’ 2x2 Tables

<table>
<thead>
<tr>
<th></th>
<th>Diseased</th>
<th>Not Diseased</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>89</td>
<td>90</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>96</td>
<td>100</td>
</tr>
</tbody>
</table>

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>a</td>
<td>b</td>
<td>a+b</td>
</tr>
<tr>
<td>No</td>
<td>c</td>
<td>d</td>
<td>c+d</td>
</tr>
<tr>
<td>Total</td>
<td>a+c</td>
<td>b+d</td>
<td>a+b+c+d</td>
</tr>
</tbody>
</table>
### Sensitivity

The proportion of people with the diagnosis (N=.....) who are correctly identified (n=.....)

Sensitivity = ..../(....+.....) = ..... = ........%
### SPECIFICITY

The proportion of people without the diagnosis (N= .......) who are correctly identified (n=......)

Specificity = ...../ (.....+.....) = ..../ ..... = ......%
### PRE-TEST PROBABILITY

<table>
<thead>
<tr>
<th>TEST</th>
<th>DI SEASE</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Total</td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
<td>b</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>a</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>89</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>c</td>
<td>d</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>96</td>
<td>100</td>
</tr>
</tbody>
</table>

In the sample as a whole, the odds (probability) of having the disease are .... or ....% (= the PRE-TEST ODDS)
### POST-TEST ODDS

In those who score positive on the test, the odds of having the disease are ..... or ........% (the POST-TEST ODDS)

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TEST</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>89</td>
<td>90</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>96</td>
<td>100</td>
</tr>
</tbody>
</table>

**DI SEASE**

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[
a+b+c+d = 100
\]

\[
a+c = 10
\]

\[
b+d = 90
\]

\[
a+b = 10
\]

\[
c+d = 90
\]
## POST-TEST ODDS

<table>
<thead>
<tr>
<th>TEST</th>
<th>Disease</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>sum</td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>

In those who score negative on the test, the odds of having the disease ...... or approximately ......%
The Diagnostic Odds Ratio is the ratio of odds of having the diagnosis given a positive test to those of having the diagnosis given a negative test.

Potentially useful as an overall summary measure, but only in conjunction with other measures (LR, sensitivity, specificity).

\[
\text{DOR} = \frac{\frac{3}{7}}{\frac{1}{89}} = \frac{0.429}{0.011} = 38.2
\]
BAYES THEOREM

POST-TEST ODDS = LIKELIHOOD RATIO \times \text{ PRE-TEST ODDS}
LIKELIHOOD RATIO AND PRE- AND POST-TEST PROBABILITIES

For a given test with a given likelihood ratio, the post-test probability will depend on the pre-test probability (that is, the prevalence of the condition in the sample being assessed)
# Sensitivity Analysis of a Diagnostic Test

<table>
<thead>
<tr>
<th>Pre-test Probability</th>
<th>Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35%</td>
<td>26% to 44%</td>
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![Graph showing sensitivity analysis with pre-test probability, likelihood ratio, and post-test probability.](image)
SENSITIVITY ANALYSIS OF A DIAGNOSTIC TEST

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<td>Pre-test probability</td>
<td>35%</td>
<td>26% to 44%</td>
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<tr>
<td>Likelihood ratio</td>
<td>5.0</td>
<td>3.0 to 8.5</td>
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Applying the 95% confidence intervals above to the nomogram, the post-test probability is likely to lie in the range 55-85%
APPLYING A DIAGNOSTIC TEST IN DIFFERENT SETTINGS

• The Positive Predictive Value of a test will vary (according to the prevalence of the condition in the chosen setting)

• Sensitivity and Specificity are usually considered properties of the *test* rather than the *setting*, and are therefore usually considered to remain constant

• However, sensitivity and specificity are likely to be influenced by complexity of differential diagnoses and a multitude of other factors (cf spectrum bias)