DIAGNOSTIC STUDIES

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WHY SCREENING, DIAGNOSTIC AND PROGNOSTIC TESTS MATTER

- Diagnosis is the first and important step in the pathway to correct treatment
- Early and rapid diagnosis can reduce morbidity, improve patient outcomes, and reduce cost of care
- Tests can
  - identify disease & risk factors
  - predict prognosis
  - monitor therapy over time
  - promote healthy behaviours
  - tailor therapies (i.e. personalized medicine)
  - used for surveillance
EXPLOSION OF DIAGNOSTIC TECHNOLOGIES
This is all exciting, but…
How do we know these new tests are accurate?

- Diagnostic tests, just like drugs and vaccines, need adequate validation before they can be used on people.
  - Too many Covid19 tests have been fast-tracked to market, with little validation!
- Just like drug trials, we do diagnostic trials.
A diagnostic test is done on sick people
- patient presents with symptoms
- pre-test probability of disease is high (i.e. disease prevalence is high)

A screening test is usually done on asymptomatic, apparently healthy people
- healthy people are encouraged to get screened
- pre-test probability of disease is low (i.e. disease prevalence is low)
PROCESS OF DIAGNOSIS: ALL ABOUT PROBABILITY!

Test Threshold

0%

No Tests

Probability of Diagnosis

Need to Test

Treatment Threshold

100%

Treat
The Perfect Diagnostic Test

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Disease</td>
<td>Disease</td>
</tr>
</tbody>
</table>
Variations in Diagnostic Tests

Overlap

Range of Variation in Disease free

Range of Variation in Diseased
So, cut-points matter a lot!

- Many tests produce continuous numbers, and doctors tend to use cut-points to make decisions.
- Cut-points are a compromise – they are not perfect.
- Same test can produce different results, based on cut-points used.
- Cut-points can change over time.
There is no perfect test!

All we can hope to do is increase or decrease probabilities, and Bayes' theorem helps with this process.
Bayes' Theory

What you thought before + New information = What you think now

pre-test probability

Post-test odds = Pre-test odds x Likelihood ratio
Bayesian approach to diagnosis

- An accurate test will help reduce uncertainty
- The pre-test probability is revised using test result to get the post-test probability
- Tests that produce the biggest changes from pretest to post-test probabilities are most useful in clinical practice [very large or very small likelihood ratios]
Steps in evaluating a diagnostic test

- Define gold standard or reference standard
- Recruit consecutive patients in whom the test is indicated (in whom the disease is suspected)
- Perform gold standard on all, to identify true disease status
- Perform test on all and classify them as test positives or negatives
- Set up 2 x 2 table and compute:
  - Sensitivity
  - Specificity
  - Predictive values
Imagine a hypothetical population
(some with disease and others without)
If a test was positive in everyone, what would you make of this test?
What about this scenario?

- ○ is a well person
- ● is a person with a disease
- ☐ is a negative test result
- □ is a positive test result
In reality, most tests will produce these sorts of results
Let us now quantify test accuracy

• Diagnostic 2 X 2 table:

<table>
<thead>
<tr>
<th></th>
<th>Disease +</th>
<th>Disease -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test +</td>
<td>True Positive</td>
<td>False Positive</td>
</tr>
<tr>
<td>Test -</td>
<td>False Negative</td>
<td>True Negative</td>
</tr>
</tbody>
</table>
## Sensitivity

**[true positive rate]**

<table>
<thead>
<tr>
<th></th>
<th>Disease present</th>
<th>Disease absent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test positive</strong></td>
<td>True positives</td>
<td>False positives</td>
</tr>
<tr>
<td><strong>Test negative</strong></td>
<td>False negative</td>
<td>True negatives</td>
</tr>
</tbody>
</table>

The proportion of patients with disease who test positive = \( P(T^+|D^+) = TP / (TP+FN) \)
The proportion of patients without disease who test negative: $P(T|D-) = \frac{TN}{TN + FP}$.
Predictive value of a positive test

<table>
<thead>
<tr>
<th></th>
<th>Disease present</th>
<th>Disease absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test positive</td>
<td>True positives</td>
<td>False positives</td>
</tr>
<tr>
<td>Test negative</td>
<td>False negative</td>
<td>True negatives</td>
</tr>
</tbody>
</table>

Proportion of patients with positive tests who have disease = \( P(D|T+) = \frac{TP}{TP+FP} \)
## Predictive value of a negative test

<table>
<thead>
<tr>
<th></th>
<th>Disease present</th>
<th>Disease absent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test positive</strong></td>
<td>True positives</td>
<td>False positives</td>
</tr>
<tr>
<td><strong>Test negative</strong></td>
<td>False negative</td>
<td>True negatives</td>
</tr>
</tbody>
</table>

Proportion of patients with negative tests who do not have disease = \( P(D^-|T^-) = \frac{TN}{TN+FN} \)
103 specimens from 48 patients with PCR confirmed SARS-CoV-2 infections and 153 control specimens were analyzed using SARS-CoV-2 serologic assays by Abbott and EUROIMMUN (EI).
**EUROIMMUN TEST**

### Gold Standard

<table>
<thead>
<tr>
<th>Antibody test</th>
<th>PCR+ Covid cases</th>
<th>Pre-2019 negative controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>41</td>
<td>3</td>
</tr>
<tr>
<td>Negative</td>
<td>7</td>
<td>47</td>
</tr>
</tbody>
</table>

Total:
- 48 (PCR+ Covid cases)
- 50 (Pre-2019 negative controls)
- 98 (Total)

**Sensitivity = 85%**

**Specificity = 94%**

**Pos Predictive Value = 93%**

**Neg Predictive Value = 87%**

Disease prevalence in this study ~50% (48 / 98)
What happens when we use this test to measure sero-prevalence?

Let’s imagine the population prevalence is modest (e.g. 30%)

If 1000 people were tested in this population, with the 85% sensitivity and 94% specificity we have for Euroimmun test, we should get this 2x2 table:

<table>
<thead>
<tr>
<th></th>
<th>Disease +</th>
<th>Disease -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody test</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>+</td>
<td>255</td>
<td>42</td>
</tr>
<tr>
<td>-</td>
<td>45</td>
<td>658</td>
</tr>
</tbody>
</table>

| 300 | 700 | 1000 |

\[
\begin{array}{ccc}
255 & 42 & 297 \\
45 & 658 & 703 \\
300 & 700 & 1000 \\
\end{array}
\]

Pos Predictive Value = 86% (less than 93% when prevalence was 50%)
Neg Predictive Value = 94%
What happens when we use this test to measure sero-prevalence?

• Let’s imagine the population prevalence is low (e.g. 2%)
  • If 1000 people were tested in this population, with the 85% sensitivity and 94% specificity we have for Euroimmun test, we should get this 2x2 table:

<table>
<thead>
<tr>
<th></th>
<th>+</th>
<th>-</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>17</td>
<td>59</td>
<td>76</td>
</tr>
<tr>
<td>-</td>
<td>3</td>
<td>921</td>
<td>924</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>+</th>
<th>-</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>20</td>
<td>980</td>
<td>1000</td>
</tr>
</tbody>
</table>

Pos Predictive Value = 22% (for 1 true positive, there will be nearly 4 false-positives)
Neg Predictive Value = ~100%
Sources of bias in diagnostic studies

• Bias due to an inappropriate reference standard
• Spectrum bias
• Verification (work-up) bias
  • Partial verification bias
  • Differential verification bias
• Review bias (lack of blinding)
• Incorporation bias
Diagnostic tests are not perfect & need to be validated carefully before use

Diagnostic and screening tests are very different and should not be confused

Doctors and patients need to understand that all tests have their inherent error (i.e. false positives and false negatives)

Tests should always be interpreted in context (hospital use vs prevalence surveys)

Tests should be avoided unless there is a clear indication