Lecture 5 – Clinical Testing

Understanding the process of diagnosis and clinical testing

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Objectives - Concepts

1. To understand the concept of 'testing'
2. The 2 x 2 table
3. The concept of the 'gold standard'
4. Sensitivity (Se) and Specificity (Sp)
5. Tradeoff in Se and Sp, ROC curves
6. Predicted Values (PVP and PVN)
7. The importance of Prevalence
8. The concept of Bayes' theorem (probability revision)

Objectives - Skills

1. Construct a 2 x 2 table
2. Define, calculate, and interpret Se & Sp
3. Using the 2 x 2 table define, calculate, and interpret PVP & PVN for any combination of Se, Sp, and Prevalence
4. Begin to integrate the concept of prior probability or prevalence into diagnostic testing (Bayes theorem)
Riding a bike vs. mastering the balance beam......

Clinical Diagnosis and Clinical Testing

- Diagnosis: the process of discovering a patient's underlying disease status by:
  - ascertaining the patient's history, signs and symptoms, choosing appropriate tests, interpreting the results, and making correct conclusions.
  - Highly complicated, not well understood process.

- Testing: the application of "clinical test information" to infer disease status:
  - "Clinical test information" refers to any piece of information not just laboratory or diagnostic tests!!

Fig 1. The 2 x 2 table
Relationship between Diagnostic Test Result and Disease Status

<table>
<thead>
<tr>
<th>DISEASE STATUS</th>
<th>PRESENT (D+)</th>
<th>ABSENT (D-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POSITIVE (T+)'s</td>
<td>TP</td>
<td>FP</td>
</tr>
<tr>
<td>TEST RESULT</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>NEGATIVE (T-)</td>
<td>FN</td>
<td>d TN</td>
</tr>
</tbody>
</table>
The Gold Standard (or Referent Standard)

- **Define the accepted standard for determining the true disease status**
- Want to know the disease status with certainty but this is frequently not possible because:
  - Gold standard test is difficult, expensive, risky, unethical, or simply not possible
    - e.g., DVT requires leg venogram (difficult, expensive)
    - e.g., vCJD requires autopsy (not possible)
  - Frequently resort to using an imperfect proxy as a referent standard
    - e.g., Ultrasound and/or 3-month follow-up in place of venogram to confirm presence/absence of DVT.

Sensitivity (Se) & Specificity (Sp)

- Interpretation of diagnostic tests is concerned with comparing the relative frequencies and "costs" of the incorrect results (FNs and FPs) versus the correct results (TPs and TNs).
- Degree of overlap is a measure of the test's effectiveness or discriminating ability which is quantified by Se and Sp.

Fig 2. Results for a Typical Diagnostic Test Illustrating Overlap Between Disease (D+) and Non-disease (D-) Populations

[Diagram showing TN, TP, FP, FN with cut-point]

= FP

= FN

Diagnostic test result (continuous)
**Sensitivity (Se)**
- **Defn:** the proportion of individuals with disease that have a positive test result, or
  - \( Se = \frac{TP}{TP + FN} = \frac{a}{a + c} \)
- conditional probability of being test positive given that disease is present
- \( Se = P(T^+ | D^+) \)
- calculated solely from diseased individuals (LH column)
- also referred to as the true-positive rate
- a.k.a. "the probability of calling a case a case"

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**Specificity (Sp)**
- **Defn:** the proportion of individuals without disease that have a negative test result, or
  - \( Sp = \frac{TN}{TN + FP} = \frac{d}{d + b} \)
- conditional probability of being test negative given that disease is absent
- \( Sp = P(T^- | D^-) \)
- calculated solely from non-diseased individuals (RH Column)
- also referred to as the true-negative rate.
- a.k.a. "the probability of calling a control a control"
**Tests with High Sensitivity**

- Perfectly sensitive test (Se = 100%), all diseased patients test positive (no FN's)
  - Therefore all test negative patients are disease free (Tn's)
    - But typical tradeoff is a decreased Sp (many PP's)

- Highly sensitive tests are used to rule-out disease
  - If the test is negative you can be confident that disease is absent (FN results are rare)

- SnOut = if a test has a sufficiently high Sensitivity, a Negative result rules out disease

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**Fig 5. Example of a Perfectly Sensitive Test (no FN's)**

![Diagram of diagnostic test result]

- TP = true positive
- TN = true negative
- FP = false positive
- FN = false negative
- Cut-off point

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**Fig 4. D+ & D- of D-dimer whole blood assay (Staclot®RED assay) for DVT (Ref: Wallis PS, Circulation, 1993)**

<table>
<thead>
<tr>
<th></th>
<th>PRESENT (D+)</th>
<th>ABSENT (D-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POS (T+)</td>
<td>47</td>
<td>37</td>
</tr>
<tr>
<td>D-dimer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEG (T-)</td>
<td>6</td>
<td>124</td>
</tr>
</tbody>
</table>

| Se = 47/53 | Sp = 124/161 |
|           | 83%         | 77%         |

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**Matthew J. Brown**

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Clinical applications of tests with high Se

1) Early stages of a diagnostic work-up.
   - Large number of potential diseases are being considered
   - A negative result indicates a particular disease can be dropped (i.e., ruled out)

2) Important penalty for missing a disease.
   - Dangerous but treatable conditions e.g., DVT, TB, Appendicitis
   - Don't want to miss cases, hence avoid false negative results

3) Screening tests.
   - The probability of disease is relatively low (i.e., low prevalence)
   - Want to find as many asymptomatic cases as possible
     (increased yield of screening)

Table 1. Examples of Tests with High Sensitivities

<table>
<thead>
<tr>
<th>Disease/Condition</th>
<th>Test Result</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Normal Glucose</td>
<td>98%</td>
</tr>
<tr>
<td>Fracture of leg</td>
<td>Positive CT scan</td>
<td>95%</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>Absent systolic pressure</td>
<td>100%</td>
</tr>
<tr>
<td>Drug resistance</td>
<td>False Negative</td>
<td>65%</td>
</tr>
</tbody>
</table>

Tests with High Specificity

- Perfectly specific test (Sp = 100%), all non-diseased patients test negative (No FP's)
- Therefore all test positive patients have disease (TP's)
- But typical tradeoff is large number of FP's

- Highly specific tests are used to rule-in disease
  - If the test is positive you can be confident that disease is present (FP's are rare).

- SpPin = if a test has a sufficiently high Specificity, a Positive result rules in disease.
Clinical applications of tests with high Sp

1. To rule-in a diagnosis suggested by other tests
   - Specific tests are therefore used at the end of a work-up to rule-in a final diagnosis e.g. biopsy, culture.

2. False positive tests results can harm patients
   - Want to be absolutely sure that disease is present.
   - Example: the confirmation of HIV positive status or the confirmation of cancer prior to chemotherapy.

Table 2. Examples of Tests with High Specificities

<table>
<thead>
<tr>
<th>Patients without HIV disease/condition</th>
<th>...will have this test result</th>
<th>...X% of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease/condition</td>
<td>Test</td>
<td>Specificity</td>
</tr>
<tr>
<td>Alcohol dependency</td>
<td>Negative</td>
<td>99.9%</td>
</tr>
<tr>
<td>Involuntary muscle contractions</td>
<td>Negative</td>
<td>99%</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>Negative</td>
<td>99%</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Negative</td>
<td>99%</td>
</tr>
</tbody>
</table>

Mark J. Burns
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Trade off between Se and Sp

- Obviously we'd like tests with both high Se and Sp (> 95%), but this is rarely possible.
- An inherent trade-off exists between Se and Sp (if you increase one, the other must decrease).
- Whenever clinical data take on a range of values the location of the cut-point is arbitrary.
- It should depend on the purpose of the test.
- Methods exist to calculate the best cut-point based on the frequency and relative "costs" of the FN and FP results.
- Trade-off between Se and Sp is demonstrated on ROC curve (refer to course notes and PP text).

Fig 7. A ROC Curve (2-hr post-prandial blood sugar for the diagnosis of Diabetes)

Predictive Values

- In terms of conditional probabilities Se and Sp are defined as:
  - Se = P(T+=|D+), Sp = P(T-|D-)
- Problem: can only be calculated if the true disease status is known.
- But the clinician is using a test precisely because the disease status is unknown.
- So, clinician actually wants the conditional probability of disease given the test result, OR
  - P(D+|T+) and P(D-|T-)

(Place for references)
Predictive Value Positive (PVP)

- Definition: The probability of disease in a patient with a positive (abnormal) test.

\[ PVP = \frac{TP}{TP + FP} = \frac{a}{a + b} \]

- Calculated solely from test positive individuals (top row of 2 x 2 table).

- Conditional probability of being diseased given the test was positive, or PVP = P(\text{D+}|T+).

- N.B., the link between Sp and PVP via the FP rate (cell b). A highly specific test rules in disease (think Sp), PVP is maximized.

Predictive Value Negative (PVN)

- Definition: The probability of not having disease when the test result is negative (normal).

\[ PVN = \frac{TN}{TN + FN} = \frac{d}{d + c} \]

- Calculated solely from test negative individuals (bottom row of 2 x 2 table).

- Conditional probability of not being diseased given the test was negative or PVN = P(\text{D-}|T-).

- Clinically, we are also interested in the complement of the PVN i.e., 1 - PVN, which is the probability of having disease despite testing negative.

\[ 1 - PVN = P(T+|D-) \]
Fig 9. The PVP and P VN of D-dimer whole blood assay (SimpliRED assay) for DVT (data: Wells FS. Circulation, 1995. Prevalence = 5%).

<table>
<thead>
<tr>
<th>DVT</th>
<th>PRESENT (D+)</th>
<th>ABSENT (D-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POS (T+)</td>
<td>47</td>
<td>37</td>
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<tr>
<td>NEG (T-)</td>
<td>6</td>
<td>124</td>
</tr>
</tbody>
</table>

PVP = 47/84 = 56%
P VN = 124/130 = 95%

N = 55
N = 161
N = 214
Se = 89%
Sp = 77%

Prevalence
- the proportion of the total population tested that have disease, or
- \[ P = \frac{TP + FN}{TP + FN + FP + TN} = \frac{a + c}{a + b + c + d} \]
- Equivalent names:
  - prior probability, the likelihood of disease, prior belief, prior odds, pre-test probability, and pre-test odds.
- So what? Why is this so important?

Fig 10. The PVP and P VN of D-dimer whole blood assay (SimpliRED assay) for DVT (data: Wells FS. Circulation, 1995). Prevalence = 5%.

<table>
<thead>
<tr>
<th>DVT</th>
<th>PRESENT (D+)</th>
<th>ABSENT (D-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POS (T+)</td>
<td>10</td>
<td>47</td>
</tr>
<tr>
<td>D-dimer</td>
<td>1</td>
<td>156</td>
</tr>
</tbody>
</table>

PVP = 10/157 = 18%
P VN = 156/157 = 99.4%

N = 11
N = 203
N = 214
Se = 89%
Sp = 77%
Importance of Prevalence or Prior Probability

- Has a dramatic influence on predictive values
- Prevalence can vary widely from hospital to hospital, clinic to clinic, or patient to patient
- The same test (meaning the same Se and Sp) when applied under different scenarios (meaning different prevalence’s) can give very different results (meaning different PVP and PVN!)
- N.B. Prior probability represents what the clinician believes (prior belief or clinical suspicion)
  - set by considering the practice environment, patient’s history, physical examination findings, experience and judgment etc.

Bayes' Theorem

- Bayes' theorem = a unifying methodology for interpreting clinical test results.
- Bayes' formulae or equations are used to calculate PVP and PVN for any combination of Se, Sp, and Prev.

\[
PVP = \frac{[Sp \cdot Prev]}{[Se \cdot Prev] + [(1 - Sp) \cdot (1 - Prev)]}
\]

\[
PVN = \frac{[Sp \cdot (1 - Prev)]}{[Sp \cdot (1 - Prev)] + [(1 - Sp) \cdot Prev]}
\]
What is Bayes’ Theorem all about?
It revises disease estimates in light of new test information

Use of Bayes’ Formula

Before-test
After - test
After + test

0
0.5
1.0
Probability of Disease

Summary
I. Test Operating Characteristics

<table>
<thead>
<tr>
<th>Also Defined</th>
<th>Derived From</th>
<th>Useful Result</th>
<th>Most Affects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>true positive rate</td>
<td>patients with disease</td>
<td>negative predictive value</td>
</tr>
<tr>
<td>Specificity</td>
<td>true negative rate</td>
<td>patients without disease</td>
<td>positive predictive value</td>
</tr>
</tbody>
</table>

II. Testing Situations

Likely disease prevalence

Use a test which:

Rule Out
- low
- negative predictive value
- Sensitive

Rule In
- high
- positive predictive value
- Specific