Effectiveness of Screening

Sources of bias in evaluating screening programs:

1. Self-selection bias (volunteer bias)
2. Lead time bias
3. Length bias

Lead time definition

- Interval between detection of a disease at screening & when it would be detected due to the development of symptoms.
- Amount of time by which the diagnosis has been advanced as a result of screening.
- Depends on how diseases progress from pre to clinical but also how soon the screening is performed after the preclinical conditions become detectable.
Bias in the evaluation of screening

- Patient self-selection bias.

- Lead time bias.

- Length bias.

Bias in the evaluation of screening (cont.)

- Patient self-selection bias.
  - Those who participate are likely to be different:
    - better health,
    - low mortality rates,
    - the ‘worried well’.
  
  - The direction of potential bias difficult to predict and magnitude difficult to quantify.

Bias in the evaluation of screening (cont.)

- Lead time bias.
  - Lead time is the interval between “diagnosis” of disease at screening and when it would have been detected from clinical symptoms.
  - Lead time Bias: Survival may erroneously appear to be increased among screened-detected cases simply because the diagnosis was made earlier in the course of disease.
Bias in the evaluation of screening (cont.)

• **Length bias.**
  - Overrepresentation among screen-detected cases of those with long preclinical phase and thus a more favorable prognosis.
  - Those with a long pre-clinical phase are more readily detectable by screening than more rapidly progressing cases with a short pre-clinical phase.
  - Difficult to quantify.

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**DEFINITIONS. Accuracy Indices of a test.**

**Sensitivity and Specificity**

- **Sensitivity**
  - Likelihood of a **positive test** among those **with** the condition \( (T^+ \; D^+ \) )
  - Or
  - Probability of **testing positive** if the disease is **truly present**. Calculated by \( \frac{a}{a + c} \)

- **Specificity**
  - Likelihood of a **negative test** among those **without** the condition \( (T^- \; D^-) \)
  - Or
  - Probability of **screening negative** if the disease is **truly absent**. Calculated by \( \frac{d}{b + d} \)
Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

- **PPV**
  - Likelihood of having the condition among those with a positive test \((Dx^+ T^+)\) or
  - Probability that a person actually has the disease given that he/she tests positive. Calculated by: \(a/(a + b)\)

- **NPV**
  - Likelihood of not having the condition among those with a negative test \((Dx^- T^-)\) or
  - Probability that an individual is truly disease-free given a negative screening test. Calculated by: \(d/(c + d)\)

<table>
<thead>
<tr>
<th>Disease present</th>
<th>Disease absent</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test positive</td>
<td>True Positive</td>
<td>False Positive</td>
</tr>
<tr>
<td>Test Negative</td>
<td>False Negative</td>
<td>True Negative</td>
</tr>
<tr>
<td>Totals</td>
<td>(a+c)</td>
<td>(b+d)</td>
</tr>
</tbody>
</table>

Validity of Screening Tests

<table>
<thead>
<tr>
<th></th>
<th>Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>132</td>
</tr>
<tr>
<td>Negative</td>
<td>983</td>
</tr>
<tr>
<td>Positive Screened</td>
<td>45</td>
</tr>
<tr>
<td>Negative Screened</td>
<td>63650</td>
</tr>
</tbody>
</table>

Sensitivity: \(a / (a + c)\) = 74.6%
Specificity: \(d / (b + d)\) = 98.5%
Sensitivity, Specificity, PPV, NPV

<table>
<thead>
<tr>
<th>Disease Present</th>
<th>Disease Absent</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True positive</td>
<td>132</td>
<td>983</td>
</tr>
<tr>
<td>False positive</td>
<td>983</td>
<td>45</td>
</tr>
<tr>
<td>Test Negative</td>
<td>False negative</td>
<td></td>
</tr>
<tr>
<td>False negative</td>
<td>45</td>
<td>63650</td>
</tr>
<tr>
<td>True negative</td>
<td>63650</td>
<td>63650</td>
</tr>
<tr>
<td>Totals</td>
<td>177</td>
<td>64633</td>
</tr>
</tbody>
</table>

Sensitivity = $a/(a+c) = 132/177 = 74.6\%$

Specificity = $d/(b+d) = 63650/64633 = 98.5\%$

PPV = $a/(a+b) = 132/1115 = 11.8\%$

NPV = $d/(c+d) = 63650/63695 = 99.9\%$

Validity of Screening Tests

Sensitivity and Specificity

- Would be desirable to have a test both highly sensitive and highly specific.
- Usually not possible, there is generally a tradeoff.
- Tradeoff is due to the fact that for many tests there are
  - some people clearly normal,
  - some clearly abnormal and
  - some who fall into the grey zone.
- In these situations the cutoff between normal and abnormal is an arbitrary decision.

Sensitivity and Specificity (cont.)

- Altering the criterion of positivity or abnormality influence both.
- Lowering the criterion of positivity will mean that more people who actually have the disease will be test-positive (increase sensitivity)
- But so will a number of people who do not have the disease (decrease specificity)
Sensitivity and Specificity (cont.)

• Conversely, making the criterion more stringent will mean that
  • a greater proportion of those who test negative will actually not have the
disease (increased specificity), but
  • a larger number of true cases will also be missed (decreased
sensitivity).

Validity of Screening Tests

Setting the criterion for positivity: simple situation: Bi-modal distribution

Question: What is the best cutpoint?

Sensitivity and Specificity (cont.)

• Hypothetical distribution of results on EIA for HIV by actual antibody status
Sensitivity and Specificity (cont.)

- Way of addressing the problem of trade-off between sensitivity and specificity:
  - use results of several screening tests together,
  - administered in parallel or in series.
- One example of a test in parallel: deep vein thrombosis.
- Examples of tests in series are screening for syphilis or HIV.

- Examples:
  - Syphilis: Venereal Disease Research Laboratory (VDRL) is quite sensitive; you obtain many false positives. Then use Fluorescent Treponemal Antibody Absorption (FTA-ABS) test, which has a high specificity as well as sensitivity.
  - HIV: Elisa (enzyme-linked immunosorbent assay- EIA) and then Western blot confirmatory testing.

- Decision regarding specific criteria for acceptable levels of sensitivity and specificity involves weighing the consequences of
  - leaving cases undetected (false negatives) against
  - erroneously classifying healthy persons as diseased (false positive).
Sensitivity and Specificity (cont.)

• Sensitivity should be increased when:
  • penalty associated with missing a case is high (serious disease has treatment available - PKU),
  • when the disease can be spread (syphilis or gonorrhea),
  • when you are screening to estimate prevalence/incidence of a condition in a population (FN result in underestimation of rates), or
  • when more diagnostic evaluations are associated with minimum cost or risk (hypertension).

• Specificity should be increased when
  • the costs or risks associated with further diagnostic techniques are substantial:
    • breast cancer, definitive diagnostic evaluation is a biopsy.
  • In this circumstance it must be made clear to those screened negative that there is not a guarantee of being disease-free but rather that the probability of having disease is low.

Reliability of Screening Tests

Sources of variability that can affect the reproducibility of results of a screening test:

1. Biological variation (e.g. blood pressure, cholesterol)
2. Reliability of the instrument itself
3. Intra-observer variability (differences in repeated measurement by the same screener)
4. Inter-observer variability (inconsistency in the way different screeners apply or interpret test results)
Measuring the performance (yield) of a test

- The proportion of persons who screen positive on the test who actually have D
  - Predictive Value Positive (PV+ or PPV)
- The proportion of persons who screen negative on the test who are actually free of the D
  - Predictive Value Negative (PV- or NPV)

<table>
<thead>
<tr>
<th>True Disease Status</th>
<th>+</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>-</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

Performance (Yield)

Positive predictive value (PPV): Among persons who test positive, the probability that a person actually has the disease: \[ PPV = \frac{a}{a + b} \]

Negative predictive value (NPV): Among persons who test negative, the probability that a person does not have the disease: \[ NPV = \frac{d}{c + d} \]
Performance (Yield)

<table>
<thead>
<tr>
<th>True Disease Status</th>
<th>+</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results of Screening Test</td>
<td>400</td>
<td>995</td>
</tr>
<tr>
<td>-</td>
<td>100</td>
<td>98,905</td>
</tr>
</tbody>
</table>

Sensitivity: \( \frac{a}{a + c} = \frac{400}{400 + 100} = 80\% \)
Specificity: \( \frac{d}{b + d} = \frac{98,905}{995 + 98,905} = 99\% \)
PPV: \( \frac{a}{a + b} = \frac{400}{400 + 995} = 29\% \)
NPV: \( \frac{d}{c + d} = \frac{98,905}{100 + 98,905} = 99.9\% \)

Example: Performance (Yield)

<table>
<thead>
<tr>
<th>True Disease Status</th>
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<th>-</th>
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</thead>
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<tr>
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<td>400</td>
<td>995</td>
</tr>
<tr>
<td>-</td>
<td>100</td>
<td>98,905</td>
</tr>
</tbody>
</table>

PPV: \( \frac{a}{a + b} = \frac{400}{400 + 995} = 28.6\% \)
NPV: \( \frac{d}{c + d} = \frac{98,905}{100 + 98,905} = 99.9\% \)
Prevalence=\( \frac{500}{100,400} \times 100 = 0.498\% \)
 or
4.96 per 1000

Performance (yield)

<table>
<thead>
<tr>
<th>Prevalence (%)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>90%</td>
<td>95%</td>
<td>1.8%</td>
</tr>
<tr>
<td>1.0</td>
<td>90%</td>
<td>95%</td>
<td>15.4%</td>
</tr>
<tr>
<td>5.0</td>
<td>90%</td>
<td>95%</td>
<td>48.6%</td>
</tr>
<tr>
<td>50.0</td>
<td>90%</td>
<td>95%</td>
<td>94.7%</td>
</tr>
</tbody>
</table>

Prevalence (%) Sensitivity Specificity PPV
0.1 90% 95% 1.8%
1.0 90% 95% 15.4%
5.0 90% 95% 48.6%
50.0 90% 95% 94.7%
Factors that influence PPV and NPV

1. The more specific the test, the higher the PPV
2. The more sensitive the test, the higher the NPV
3. The higher the prevalence of pre-clinical disease in the screened population, the higher the PPV

### Performance (yield)

#### Effect of Prevalence on PPV & NPV

Assuming test sensitivity and specificity both = 95%

**Prevalence = 10%**

<table>
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<th>Disease Absent</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test positive</strong></td>
<td>9,500</td>
<td>4,500</td>
<td>14,000</td>
</tr>
<tr>
<td><strong>Test Negative</strong></td>
<td>500</td>
<td>85,500</td>
<td>86,000</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td>10,000</td>
<td>86,000</td>
<td>100,000</td>
</tr>
</tbody>
</table>

PPV = 9,500/14,000 = 67.9%
NPV = 85,500/86,000 = 99.4%

**Prevalence = 1%**

<table>
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<th>Disease Absent</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test positive</strong></td>
<td>950</td>
<td>4,950</td>
<td>5,900</td>
</tr>
<tr>
<td><strong>Test Negative</strong></td>
<td>50</td>
<td>94,050</td>
<td>94,100</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td>1,000</td>
<td>94,100</td>
<td>100,100</td>
</tr>
</tbody>
</table>

PPV = 950/5,900 = 16.1%
NPV = 94,050/94,100 = 99.9%
Summary of Screening for disease detection

- Relatively quick way of detecting potential disease in a population before it manifests.

- Validity measured by
  - sensitivity and
  - specificity
  
  and depends on a Gold Standard measure.

Summary of Screening for disease detection

- Precision has to do with consistency or stability of results (errors due to method, subject and/or observer variability).

- Have benefits and risks.

- Efficacy determined by RCT.

- Other important issues are the biases:
  - volunteer,
  - lead time and
  - length time