Efficient design and analysis of clinical value for paired medical tests at single and serial time points

Timothy Chang, Richard Chappell
Institute for Clinical and Translational Research
University of Wisconsin – Madison
MD/PhD Candidate, G2
Medical testing for screening and diagnostics

• Biomarkers

• Genetics

• Imaging

• Computational modeling

Why are these not used more in practice?
Why do we need a RCT if a new medical test has higher accuracy?

Do we have efficacious treatment for these new correctly diagnosed patients?

Question: Which medical test has better clinical value?
Randomized Clinical Trials Comparing Two Medical Tests

Randomized Clinical Trials Comparing Two Medical Tests

Examples

- MINDACT (Microarray in Node Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy Trial)
  - RCT for Mammaprint (70 gene sig for relapse in early stage breast cancer)

McDermott, NEJM. Jan 2011; clinicalTrials.gov NCT00433589
RCT setup

- Medical test 1, Medical Test 2
- (+) → Tx A, (-) → Tx B
  - Tx A was tested on the currently identifiable (+) patients
- Assumptions: no gold standard, order medical test irrelevant
- Outcome (binary): 5 year survival

Test 1 result | Test 2 result
---|---
$n_1$ + | -$  \\n$n_2$ - | +

$\frac{1}{2}n_1$ + | -  \\n$\frac{1}{2}n_2$ - | +

($+$) Tx A tested & effective

All +
1. Statistical Analysis: Treatment

Tx A versus Tx B

Question: For discordant patients, which treatment is better?

(Ligmer & Bossuyt, Evidence Base of Clinical Diagnosis, 2009)
2. Statistical Analysis: Treatment Effect of Test results

\[ n_1 + | - \text{ versus } n_2 - | + \]

When patients with one discordant result are randomly treated with A or B, does \(+ | -\) (+ Test 1) have better outcomes than \(- | +\) (+ Test 2)?

(Ligmer & Bossuyt, Evidence Base of Clinical Diagnosis, 2009)
3. Statistical Analysis: Clinical pathway (strategy based on test method)

With appropriate treatment does Test 1 have better outcomes than Test 2?

<table>
<thead>
<tr>
<th>Test 1 result</th>
<th>Test 2 result</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n_1$ +</td>
<td>$n_2$ -</td>
</tr>
</tbody>
</table>

(Ligmer & Bossuyt, Evidence Base of Clinical Diagnosis, 2009)
### 3. Statistical Analysis: Clinical pathway (strategy based on test method)

**Another view**

<table>
<thead>
<tr>
<th>Strategy based on Medical Test 1</th>
<th></th>
<th>Strategy based on Medical Test 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 2 Tx Favorable Poor outcome</td>
<td>1 2 Tx Favorable Poor outcome</td>
<td></td>
</tr>
<tr>
<td>+ - A Favorable outcome</td>
<td>- + A Favorable outcome</td>
<td></td>
</tr>
<tr>
<td>- + B Poor outcome</td>
<td>+ - B Poor outcome</td>
<td></td>
</tr>
</tbody>
</table>

**Absolute risk difference of clinical pathway Test 1 compared to clinical pathway Test 2**

\[
\text{Difference in favorable outcome rate, after correcting for frequency of discordant} = \text{Absolute risk difference of clinical pathway Test 1 compared to clinical pathway Test 2}
\]

Note: To calculate the RR or total risk, need outcome rate for concordant group

*(Ligmer & Bossuyt, Evidence Base of Clinical Diagnosis, 2009)*
3. Clinical Pathway - Example

5% discordant rate

\[ n_1 (+|-) = 22, \quad \frac{1}{2} n_1 (+|-) = 11 \]

\[ n_2 (-|+) = 200, \quad \frac{1}{2} n_2 (-|+) = 100 \]

Total patient for each clinical pathway = 111

<table>
<thead>
<tr>
<th>Strategy based on Medical Test 1</th>
<th>Strategy based on Medical Test 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  2  Tx</td>
<td>Favorable outcome</td>
</tr>
<tr>
<td>+  -  A</td>
<td>10</td>
</tr>
<tr>
<td>-  +  B</td>
<td>50</td>
</tr>
</tbody>
</table>

60/111 = 0.54 favorable outcome

100/111 = 0.90 favorable outcome

36% absolute difference risk difference in favor of Test 2 for discordant \times 5\% discordant rate = 1.8\% absolute risk different in favor of Test 2
Paired Diagnostic tests with 3 \((k)\) treatment options

<table>
<thead>
<tr>
<th>Medical Test 1</th>
<th>Medical Test 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tx A</strong></td>
<td><strong>Tx A</strong></td>
</tr>
<tr>
<td>Same</td>
<td>A/B</td>
</tr>
<tr>
<td><strong>Tx B</strong></td>
<td><strong>B/A</strong></td>
</tr>
<tr>
<td>B/A</td>
<td>Same</td>
</tr>
<tr>
<td><strong>Tx C</strong></td>
<td><strong>C/A</strong></td>
</tr>
<tr>
<td>C/A</td>
<td>C/B</td>
</tr>
<tr>
<td></td>
<td>Same</td>
</tr>
</tbody>
</table>

Strategy based on Medical Test 1

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>Tx</th>
<th>Favorable outcome</th>
<th>Poor outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>C</td>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>A</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>C</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>A</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>B</td>
<td>C</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Strategy based on Medical Test 2

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>Tx</th>
<th>Favorable outcome</th>
<th>Poor outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>A</td>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>A</td>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>B</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>B</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>C</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>C</td>
<td>C</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Same Analysis 2 test, 2 treatment
Serial Medical Testing

- Serial Screening (mammography every 2 year)
- Therametrics – quantification of therapeutic parameters in management of disease (viral load HIV\textsuperscript{(Reed 1996)}, serum c-erbB-2 breast cancer\textsuperscript{(Fehm 1997)})
Serial Medical Testing

- Serial Screening (mammography every 2 year)
- Therametrics – quantification of therapeutic parameters in management of disease (viral load HIV\textsuperscript{(Reed 1996)}, serum c-erB-2 breast cancer\textsuperscript{(Fehm 1997)})

\[
\begin{align*}
\frac{1}{2}n_1 &+ | - \\
\frac{1}{2}n_2 &- | +
\end{align*}
\]

Same Analysis as 2 test, k treatment
Future direction

• This design should be performed even if a new test has the same sensitivity, but is cheaper/easier to conduct, etc.
• Continuous outcome with and without censoring
• Non-inferiority
Thank You

Contributors and Advisers
Richard Chappell
Michael Coen
David Page
Dave Demets

Support
UW MSTP
UW ICTR (TL1)