Correlation between biomarkers and clinical measures

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Definitions

Biomarkers (or biological marker)
- Parameters that are objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention.

Clinical measures
- Assessment of how the patient feels or functions (e.g. pain, hospital admission, surgery, death)
- Often not fully objective (the mind of the evaluator or patient can be involved)
Examples diseases and biomarkers

<table>
<thead>
<tr>
<th>Disease</th>
<th>Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>LDL cholesterol</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Fasting glucose, A1C, Insulin resistance</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Polyps</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>PSA</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Bone mineral density</td>
</tr>
<tr>
<td>Dementia</td>
<td>Mild cognitive impairment</td>
</tr>
</tbody>
</table>
## Characteristics of a good biomarker

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Property</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific</td>
<td>To a particular disease</td>
</tr>
<tr>
<td>Sensitive</td>
<td>Easily quantifiable</td>
</tr>
<tr>
<td>Predictive</td>
<td>Relevant to disease progression or treatment</td>
</tr>
<tr>
<td>Robust</td>
<td>Fast, simple, and cheap analysis</td>
</tr>
<tr>
<td>Stable</td>
<td>Equal concentrations at any time of day</td>
</tr>
<tr>
<td>Non-invasive</td>
<td>Samples easily acquired (blood, urine, etc)</td>
</tr>
<tr>
<td>Preclinical and clinical</td>
<td>Valid in animal/cell human models</td>
</tr>
<tr>
<td>importance</td>
<td></td>
</tr>
</tbody>
</table>
Biomarkers vs clinical outcomes

Biomarkers

- Repeated measurements possible
- Usually cheap
- Often high content information
- Often give rapid indication of response
- Can be of prognostic or diagnostic value

Clinical outcome

- Subjective (e.g. pain)
- Often only happens once (e.g. death)
- Can take many years for differences to be evident
Drug Treatment

Disease → Pathology → Illness

- Disease Modifying: (weeks or months)
- Symptomatic: (months, years, decades)

Biomarker: e.g. tumour size
Outcome: e.g. death
Surrogate endpoints

- U.S. National Institutes of Health defines surrogate endpoints as “biomarkers intended to substitute for a clinical endpoint”

- It may be related to the clinical (true) endpoint, but the relationship between the two may not be direct

- A surrogate endpoint is used when the primary endpoint is undesired (e.g. death), or when the number of events is very small, making it unpractical to conduct a clinical trial to gather a significant number of endpoints.
  - Example hypertension
## Examples

<table>
<thead>
<tr>
<th>Medical Disease</th>
<th>True Endpoint</th>
<th>Surrogate Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Disease</td>
<td>Survival Rate</td>
<td>Cholesterol Level</td>
</tr>
<tr>
<td>HIV Infection</td>
<td>Survival Rate</td>
<td>CD4 Counts</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Weight Loss, Bulging Eyeballs, Tremors</td>
<td>Serum T3 Level</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>Survival Rate</td>
<td>Tumor Shrinkage</td>
</tr>
</tbody>
</table>
Advantages of surrogate endpoints to clinical studies

- The study becomes **simpler**. As surrogates are usually measures of symptoms or laboratory biomarkers, it is easier to quantify comparisons.
- The study becomes **shorter**. It generally takes less time to see the effect of an intervention on a surrogate than on the final clinical outcome.
- The study becomes **less expensive**. Since the study duration is shorter, the cost decreases.
Ideal surrogate endpoint

One in which all mechanisms of action to the true endpoint are mediated through the surrogate endpoint.
When is a surrogate a valid substitute for the true endpoint?

- There must be evidence that the surrogate predicts the true endpoint
- The intervention’s effect on the true endpoint must be mediated through the surrogate endpoint
- A study involving the surrogate endpoint must also capture all the information on adverse effects associated with the intervention
Surrogate endpoints can be deceptive

- **Avastin**
  - Was introduced in 2004 to treat colorectal cancers.
  - The FDA approved it to treat lung cancers (2006) and also advanced breast cancer (2008).
  - Approvals were based on surrogate endpoints like decrease in tumor size.
  - Long-term studies of breast cancer: treatment did not increase lifespan, the true endpoint.
  - The drug had significant side effects such as heart failure.
Surrogate endpoints can be deceptive

- Vytorin (a combination of ezetimibe and simvastatin)
  - To help lower LDL cholesterol and fats, and raise HDL cholesterol in blood
  - Ezetimibe: reduces cholesterol absorption
  - Simvastatin: reduces amount of cholesterol made by the liver
  - Vytorin reduced blood levels of LDL cholesterol and C-reactive protein
  - It did not reduce arterial plaque buildup, did not increase survival rate
  - Reasons unclear
How surrogate endpoints fail

- The surrogate endpoint may not be on the causal pathway of the disease process
How surrogate endpoints fail

- Malocclusion
  - Angle’s Malocclusion Classification: Molar relationship is used as a measurement of effectiveness of an orthodontic treatment
  - True endpoint: esthetics or function (e.g. a nice smile or easy chewing)
  - Molar relationship is not necessarily correlated with esthetics or function
How surrogate endpoints fail

- The surrogate may mediate one pathway, but not all pathways
How surrogate endpoints fail

- Periodontitis
  - Inflammation in the periodontium
  - Treatment: mouth rinse
  - Surrogate endpoint: evaluation of the level of cytokines
  - True endpoint: tooth loss, increase in tooth mobility
  - Cytokines may be one of the causes, but the disease may be progressing through other pathways involving prostaglandins, collagenases, etc.
How surrogate endpoints fail

- The surrogate endpoint may not be on the pathway of the intervention’s effect
How surrogate endpoints fail

• Gingivitis
  – Treatment: mouth wash
  – Surrogate: Gingival index (based on gum bleeding, redness and swelling, halitosis)
  – Mouth wash may have effect on halitosis, but has no effect on gingival index.
How surrogate endpoints fail

- In the extreme case, the surrogate endpoint is on only one pathway of a disease with complex interactions between the pathways.
How surrogate endpoints fail

- Dental caries
  - Main causal factors: diet, size and shape of the teeth, pH, viscosity, buffering capacity, bacterial counts
  - True endpoint: pain, sensitivity, holes in teeth
  - Surrogate endpoint: e.g. level of bacteria
Conclusion

• In some cases, surrogate endpoints are excellent substitutes for true endpoints. In others, they are not.
• Therefore, serious consideration should be given to long-term follow-up studies of mortality and other serious adverse effects for any study that uses surrogate endpoints.
References