Statistical Considerations for BQ for Biomarker-Based Enrichment in Clinical Studies

Aug 21, 2015
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Outline

- Introduction to Enrichment in AD
- Examples in Alzheimer’s Disease and MCI or prodromal AD
- Statistical Principles
- Conclusions
Introduction – Uses of “Enrichment” Biomarkers

- **Diagnosis** is included in inclusion/exclusion criteria
- **Prognosis** may be used to separate groups or to enrich a diagnosed population
- **Prediction** of a treatment effect may depend on the putative mechanism of action
Introduction to Enrichment

Diagnosis -- Prognosis -- Prediction

What Is the Difference Between “Predictive and Prognostic Biomarkers”?

Adapted from Nils Brunner, MD, University of Copenhagen, Denmark, Connection 2009
Examples in Alzheimer’s Disease & MCI/prodromal AD

- MRI Brain Volume
- CSF Abeta42
- CSF Abeta42 to CSF tau ratio
Statistical Principles

- Sources of Variation
- Misclassification
- Sensitivity, Specificity and Predictive Value
- Disease Prevalence and Predictive Value of a Test
Sources of Variation

- Within patient variability (Day to day)
- Measurement Error
  - Instruments
  - Calibrations
  - Reading or administration errors
  - Experience of person taking measurements
  - Subject experience with measurement (learning effects)
- Between subject variability
  - Covariates
Between Subject Sources of Variation

Figure from Philip Quanjer, Em Professor of Physiology, Leiden U, Netherlands www.spirxpert.com
Between Subject Sources of Variation Can Be Reduced

Figure adapted from Philip Quanjer, Em Professor of Physiology, Leiden U, Netherlands www.spirxpert.com
Ignoring an Important Covariate Results in Misclassification

Correctly classified as Normal
Normal, classified as Abnormal without covariate
Correctly classified as Abnormal
Abnormal, classified as Normal without covariate

Figure adapted from Philip Quanjer, Em Professor of Physiology, Leiden U, Netherlands www.spirxpert.com
Random Error Results in Misclassification

Figure from Philip Quanjer, Em Professor of Physiology, Leiden U, Netherlands www.spirxpert.com
Random Error Results in Misclassification

![Graph showing frequency distribution with SDs for within and between subjects, 2½ percentile, and reference population.]

Figure from Philip Quanjer, Em Professor of Physiology, Leiden U, Netherlands www.spirxpert.com
Random Error Results in Misclassification

![Figure from Philip Quanjer, Em Professor of Physiology, Leiden U, Netherlands www.spirxpert.com](image-url)
Misclassification Rate Depends on Disease Prevalence

- Few tests are inherently dichotomous
- Continuous traits are used to categorize individuals
- This may result in substantial variation of the same diagnostic test in different populations
- Also depends on measurement error

Misclassification Rate Depends on Ratio of Between to Within Patient Variability and Prevalence

<table>
<thead>
<tr>
<th>Reference population with 2.5% abnormal observations</th>
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</thead>
<tbody>
<tr>
<td>Mean outcome measure</td>
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<tr>
<td>SD between subjects</td>
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<tr>
<td>SD within subjects</td>
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<tr>
<td>Disease prevalence %</td>
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<tr>
<td>Undetected Abnormal Cases %</td>
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</tbody>
</table>

- In early AD, within-patient variability is larger, resulting in more misclassification
Sensitivity, Specificity and Predictive Value

- Must be calculated against a “gold standard”
- In prodromal AD, the “gold standard” is future diagnosis with AD
- Other standards: Amyloid Imaging, future clinical decline, post-mortem plaque load
- Level of evidence required depends on risks and benefits
Predictive Value of a Test Varies with Prevalence

Figure from Philip Quanjer, Em Professor of Physiology, Leiden U, Netherlands www.spirxpert.com
Application to AD Biomarkers – Ideal Scenario

Diagnosis -- Prognosis -- Prediction

Adapted from Nils Brunner, MD, University of Copenhagen, Denmark, Connection 2009

What Is the Difference Between “Predictive and Prognostic Biomarkers”?
What if slow decliners respond better to treatment?

Diagnosis -- Prognosis -- Prediction?

Adapted from Nils Brunner, MD, University of Copenhagen, Denmark, Connection 2009

What Is the Difference Between “Predictive and Prognostic Biomarkers”?
Conclusions

- Biomarker Qualification requires estimation of and reduction in sources of variability
- Composites, repeated measurements and covariates may reduce variability
- Prevalence must be considered
- Biomarker validation depends on the risk/benefit of classification within the specified context of use