Predictive Drug Safety Profiling using Mechanism of Action
The Biovista COSS Platform

Introduction

COSS (Clinical Outcome Search Space) is a platform for finding new uses of compounds and assessing their risk profile based on a Mechanism of Action (MoA) approach. COSS creates multi-dimensional profiles of therapeutic compounds, as well as all known diseases and adverse effects, as well as genes, pathways and other biologically relevant 'entities'. It matches these against each other and delivers ranked recommendations to subject matter experts for further analysis. COSS is unique in that it addresses both the benefit and the risk sides of the drug development 'equation'. It is systematically used in a number of application scenarios including:

- Drug repositioning (repurposing)
- Adverse Event profiling
- Patient Cohort Analysis
- Clinical Hold events
- In-licensing due diligence
- Strategic business decision making
- and others

A major aim of COSS is to pro-actively identify potential clinical outcomes, in silico, when these have not yet happened. Here, we evaluate COSS as a platform for predicting Adverse Drug Reactions (ADRs).

Methodology

The predictive accuracy (sensitivity) of COSS was quantified through an experimental study where the ADRs reported at American Society of Clinical Oncology (ASCO) 2007 and American Academy of Neurology (AAN) 2008 were initially listed to create a rigorous sample of oncology and neurology drugs. These ADRs were then compared to the ones predicted using the methodology here, applied to literature data from 1997 onwards; PubMed was divided into five different data sets, each of which contained all abstracts published from 1976 up to five pre-selected points in time in the last decade (specifically 1997, 2000, 2002, 2005 and 2007) (see Figure 1).

The oncology sample used contained 58 drugs (53% of the 110 currently approved oncology ones), while the neurology sample contained 7 drugs. Ninety-one distinct ADRs were reported in the ASCO and AAN clinical trial abstracts for these drugs. Specificity was measured using an additional set of control drugs, known not to cause the ADRs. The rank of each of the ADRs determined by COSS for the ASCO and AAN drugs known to cause the ADR, and for the control drugs, were compared. Finally, a ROC analysis was also performed (Figure 3).

Results

Figure 2: Sensitivity of COSS in predicting ADRs at increasing values of a cutoff point.

At a cutoff point of 3% of the ranked ADRs list (8,440 ADRs from the FDA AERS database), over 70% of known ADRs are recovered. Results are shown as Median Value +/- Standard Error of the Median.

Table 1: Comparative ROC Values from diagnostic tests used in the clinic

<table>
<thead>
<tr>
<th>Condition</th>
<th>Test</th>
<th>ROC – AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>a-thalassemia</td>
<td>MCH (pg)</td>
<td>0.98</td>
</tr>
<tr>
<td>depleted iron stores</td>
<td>Ferritin</td>
<td>0.82</td>
</tr>
<tr>
<td>colorectal cancer</td>
<td>SEPT9</td>
<td>0.80</td>
</tr>
<tr>
<td>ischemic stroke</td>
<td>basic model of the Framingham</td>
<td>0.79</td>
</tr>
<tr>
<td>AE prediction</td>
<td>COSS</td>
<td>0.75</td>
</tr>
<tr>
<td>prostate cancer</td>
<td>PSA</td>
<td>0.67</td>
</tr>
<tr>
<td>mortality after an acute myocardial infarction</td>
<td>BNP</td>
<td>0.66</td>
</tr>
<tr>
<td>depleted iron stores</td>
<td>Serum iron</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Figure 3: ROC analysis of the overall performance of COSS in classifying drugs, according to their propensity to produce a pre-defined set of ADRs. The Area Under the Curve (AUC) value is 0.75 (95% confidence intervals 0.70 – 0.79).

KEY POINTS

- COSS complements current approaches used to design safer drugs and enhance current monitoring systems.
- Based on a mechanism of action profiling of drugs and compounds that bridges molecular data with clinical outcome, COSS has been successfully used to predict Adverse Drug Reactions and test for specific outcomes at the pre-clinical stage.
- Predictive accuracy tests to date suggest that COSS can support FDA and industry efforts towards more effective drug safety assessment and prediction.