Bayesian Calibration

George Hripcsak, David Madigan, Jami Jackson Mulgrave
• Reproducible, systematized, open source approach at scale

• Negative controls
  – Drugs and outcomes “known” to have no causal association
  – Literature, product labels, spontaneous reports
  – Empirical p-values

• Positive Controls
  – Inject signals onto negative controls with known effect size
  – Calibrated confidence intervals
Hypertension mono-therapy

Truven Health MarketScan CCAE. Therapies > 2 ingredients not shown
<table>
<thead>
<tr>
<th>Abdominal pain</th>
<th>Dementia</th>
<th>Ischemic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal weight gain</td>
<td>Depression</td>
<td>Kidney disease</td>
</tr>
<tr>
<td>Abnormal weight loss</td>
<td>Diarrhea</td>
<td>Malignant neoplasm</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>Edema</td>
<td>Measured renal dysfunction</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>End stage renal disease</td>
<td>Nausea</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>Fall</td>
<td>Neutropenia or agranulocytosis</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Gastrointestinal bleeding</td>
<td>Rash</td>
</tr>
<tr>
<td>Anaphylactoid reaction</td>
<td>Gout</td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>Anemia</td>
<td>Headache</td>
<td>Stroke</td>
</tr>
<tr>
<td>Angioedema</td>
<td>Heart failure</td>
<td>Sudden cardiac death</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Hemorrhagic stroke</td>
<td>Syncope</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Hepatic failure</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>Hospitalization with heart failure</td>
<td>Transient ischemic attack</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Hospitalization with preinfarction syndrome</td>
<td>Type 2 diabetes mellitus</td>
</tr>
<tr>
<td>Cardiovascular-related mortality</td>
<td>Hyperkalemia</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Chest pain or angina</td>
<td>Hypokalemia</td>
<td>Venous thromboembolic events</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>Hypomagnesemia</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>Hyponatremia</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Cough</td>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td>Decreased libido</td>
<td>Impotence</td>
<td></td>
</tr>
</tbody>
</table>
76 negative controls

Abnormal cervical smear
Abnormal pupil
Abrasion and/or friction burn of trunk without infection
Absence of breast
Absent kidney
Acid reflux
Acquired hallux valgus
Acquired keratoderma
Acquired trigger finger
Acute conjunctivitis
Amputated foot
Anal and rectal polyp
Burn of forearm
Calcaneal spur
Cannabis abuse
Cervical somatic dysfunction
Changes in skin texture
Chondromalacia of patella
Cocaine abuse
Colostomy present
Complication due to Crohn's disease
Contact dermatitis
Contusion of knee
Crohn's disease
Derangement of knee
Difficulty sleeping
Disproportion of reconstructed breast
Effects of hunger
Endometriosis
Epidermoid cyst
Feces contents abnormal
Foreign body in orifice
Ganglion cyst
Genetic predisposition
Hammer toe
Hereditary thrombophilia
Herpes zoster without complication
High risk sexual behavior
Homocystinuria
Human papilloma virus infection
Ileostomy present
Impacted cerumen
Impingement syndrome of shoulder region
Ingrowing nail
Injury of knee
Irregular periods
Kwashiorkor
Late effect of contusion
Late effect of motor vehicle accident
Leukorrhrea
Macular drusen
Melena
Nicotine dependence
Noise effects on inner ear
Nonspecific tuberculin test reaction
Non-toxic multinodular goiter
Onychomycosis due to dermatophyte
Opioid abuse
Passing flatus
Postviral fatigue syndrome
Presbyopia
Problem related to lifestyle
Psychalgia
Ptotic breast
Regular astigmatism
Senile hyperkeratosis
Somatic dysfunction of lumbar region
Splinter of face, without major open wound
Sprain of ankle
Strain of rotator cuff capsule
Tear film insufficiency
Tobacco dependence syndrome
Vaginitis and vulvovaginitis
Verruca vulgaris
Wrist joint pain
Wristdrop
**Method:** Study design (LEGEND)

**Treatment strategies:**
- Atenolol
- Nebivolol

**Causal contrasts of interest:**
- On-treatment effect
- Intent-to-treat effect

**Eligibility criteria:**
- Diagnosis of hypertension during previous 1 year
- No prior antihypertensive drug
- No prior cardiovascular outcome

**Outcome (Major Adverse Cardio-Cerebrovascular Event):**
- Hospitalized myocardial infarction, heart failure, stroke and sudden cardiac death

[https://github.com/OHDSI/LEGEND](https://github.com/OHDSI/LEGEND)
Method: LEGEND (Large-scale Evidence Generation and Evaluation in a Network of Databases)

All randomized trials

40 trials

10,278 comparisons

US Insurance databases
- IBM® MarketScan® CCAE (Commercial Claims and Encounters)
- IBM® MarketScan® MDCD (Multi-state Medicaid)
- IBM® MarketScan® MDCR (Medicare Supplemental Beneficiaries)
- Optum® Clinformatics®

Japanese insurance database
- Japan Medical Data Center (JMDC)

Korean National insurance database
- NHIS-national sample cohort (NHIS-NSC) DB

US EHR databases
- Columbia University medical Center
- Optum® PANTHER®

German EHR database
- QuintilesIMS Disease Analyzer (DA) Germany

https://github.com/OHDSI/LEGEND
Negative controls & the null distribution

CC: 2000314, CCAE, GI Bleed
Negative controls & the null distribution

CC: 2000314, CCAE, GI Bleed
Bayesian Approach

• Compute the posterior distribution of the TCO effect of interest, conditional on:
  – Directly estimated effect for the TCO
  – Estimated effects on all negative and positive controls
  – Across all databases
  – Across all “methods” (e.g. matching versus stratification)

• MCMC
One model, one database (V1)

\( \theta_0 \)  true effect size of interest
\( \theta_i \)  true effect size for the controls,  \( i = 1, \ldots, m \)
\( \hat{\theta}_i \) estimated effect sizes, \( i = 0, \ldots, m \)
\( \hat{\beta}_i = \hat{\theta}_i - \theta_i \) "estimated bias," \( i = 0, \ldots, m \)
\( E[\hat{\beta}_i] = \beta_i \) \( i = 0, \ldots, m \)
One model, many databases (V2)

Combining calibration with random effects meta-analysis
Many models, many databases (V4, BMA)

\[ p(\theta_0 | \mathcal{D}) = \sum_k p(\theta_0 | M_k, \mathcal{D}) p(M_k | \mathcal{D}) \]

where the data, \( \mathcal{D} \), comprise:

\[ \hat{\theta}_0^k, k = 1, \ldots, M, j = 1, \ldots, D \]
\[ \hat{\theta}_i^k, k = 1, \ldots, M, j = 1, \ldots, D, i = 1, \ldots, Q \]
\[ \theta_i, i = 1, \ldots, Q \]

can show that: \[ p(M_k | \mathcal{D}) \propto \prod_{i=1}^Q \prod_{j=1}^D p(\hat{\theta}_{ij}^k | \theta_i, M_k) \]

Combining calibration with random effects meta-analysis and BMA
Initial results (V1)

Figure: Optum Database Results
Root Mean Squared Error Using 95%

- CCAE
- Optum
- MDCD
- MDCR