Real-World Health Records for Pharmacovigilance

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Observation is the starting point of biological discovery.
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- Charles Darwin observed relationship between geography and phenotype
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- William McBride & Widukind Lenz observed association between thalidamide use and birth defects
The tools of observation are advancing
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  - sight, touch, hearing, smell, taste
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• Chemical and Biological augmentations
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- Chemical and Biological augmentations
  - chemical screening, microarrays, high throughput sequencing technology
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Bytes to KB
Megabytes to Terabytes
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- What’s next?
Your doctor is observing you like never before

>99% of Hospitals have Electronic Health Records

Source: CMS EHR Incentive Program data, April 2015 and CMS Provider of Services File, March 2015
• Goal: 1 billion patient records in a common data model
• ~300 million patient records integrated
• Automated tools available
But, there’s a problem…
Bias confounds observations
Discovery using the EHR

- The latest in our effort to use observational data to find and validate **drug-drug interactions**
- Estimating **disease heritability** using the 14 million patients’ medical records
Every drug order is an experiment.
Let’s focus on just one example...
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Drug-Drug Interactions
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- Understanding of DDIs may lead to better outcomes
  - precaution in prescription
  - synergistic therapies
Polypharmacy increases with age

76% of older Americans used two or more prescription drugs

Source: CDC/NCHS, National Health and Nutrition Examination Survey
More needs to be done to understand and identify drug-drug interactions
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- Clinical trials do not typically investigate drug-drug interactions
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• **Observational studies** are the only systematic way to detect drug-drug interactions
Large population databases enable DDI discovery

- Contain clinical data on millions of patients over many years
- Currently being used to establish single drug adverse events (pharmacovigilance)
- Eg. Spontaneous Adverse Event Reporting Systems
  - Collect adverse event reports for a patient (a snapshot in time)
  - Maintained by WHO > FDA > Health Canada
How to discover effects when they are not *directly* reported?
Diseases can be identified by the side effects they elicit
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Diagram:
- Diabetes
- Level of detection
- Measured minor effects
- Unmeasured severe effect
Diseases can be identified by the side effects they elicit

- physicians use observable side effects to form hypothesis about the underlying disease
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- physicians use observable side effects to form hypothesis about the underlying disease
- e.g. you can't see diabetes, but you can measure blood glucose
Severe ADE’s can be identified by the presence of more minor (and more common) side effects
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- First, identify the common side effects that are harbingers for the underlying severe AE
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- First, identify the common side effects that are harbingers for the underlying severe AE
- Then, combine these side effects together to form an “effect profile” for an
Identify acquired LQTS drug-drug interactions using Latent Signal Detection

LQTS, AFib, bradycardia, tachycardia

level of detection
measured minor effects
unmeasured severe effect

Drug-drug interactions and acquired Long QT Syndrome (LQTS)

- Prolonging the QT interval can lead to a dangerous **ventricular tachycardia**
- Drugs can cause acquired LQTS by blocking the hERG channel
- We are good at testing for single drugs
- We know almost nothing when it comes to DDIs
Latent Signal Detection of acquired LQTS

Top Prediction:
Ceftriaxone + Lansoprazole

- Ceftriaxone — common in-patient cephalosporin antibiotic
- Lansoprazole — proton-pump inhibitor used to treat GERD, one of the most commonly taken drugs in the world

Lorberbaum, et al. JACC (2016)
Side Effect Profile

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Side Effect Profile

Ceftriaxone + Lansoprazole

FAERS

Ceftriaxone + Lansoprazole

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FAERS

Ceftriaxone + Lansoprazole

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Electronic Health Records

Ceftriaxone + Lansoprazole

Cefuroxime + Lansoprazole

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Ceftriaxone + Lansoprazole

Cefuroxime + Lansoprazole

Electronic Health Records

Lorberbaum, et al. JACC (2016)
Automated Patch Clamp

• Collaboration with Rocky Kass (CUMC Pharmacology Dept.)

• Take HEK293 cells over-expressing the hERG channel

• Perform a single-cell patch clamp experiment
  • control
  • ceftriaxone alone
  • lansoprazole alone
  • combination of ceftriaxone and lansoprazole

Voltage protocol: step to +40mV followed by a return to -40mV

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Ceftriaxone + Lansoprazole

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Lorberbaum, et al. JACC (2016)
Computational model of human ventricular myocyte

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- Wildtype channel
- 1μM Lansoprazole + 100μM Ceftriaxone (10% block)
- 10μM Lansoprazole + 100μM Ceftriaxone (55% block)

most common at CUMC

10ms longer

Lorberbaum, et al. JACC (2016)
Guess who just learned about crypto? The world’s first blockchain primer for kids drops 10.30.18

a children’s book by Nick & Noah

More at nickandnoah.com
Thank you

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