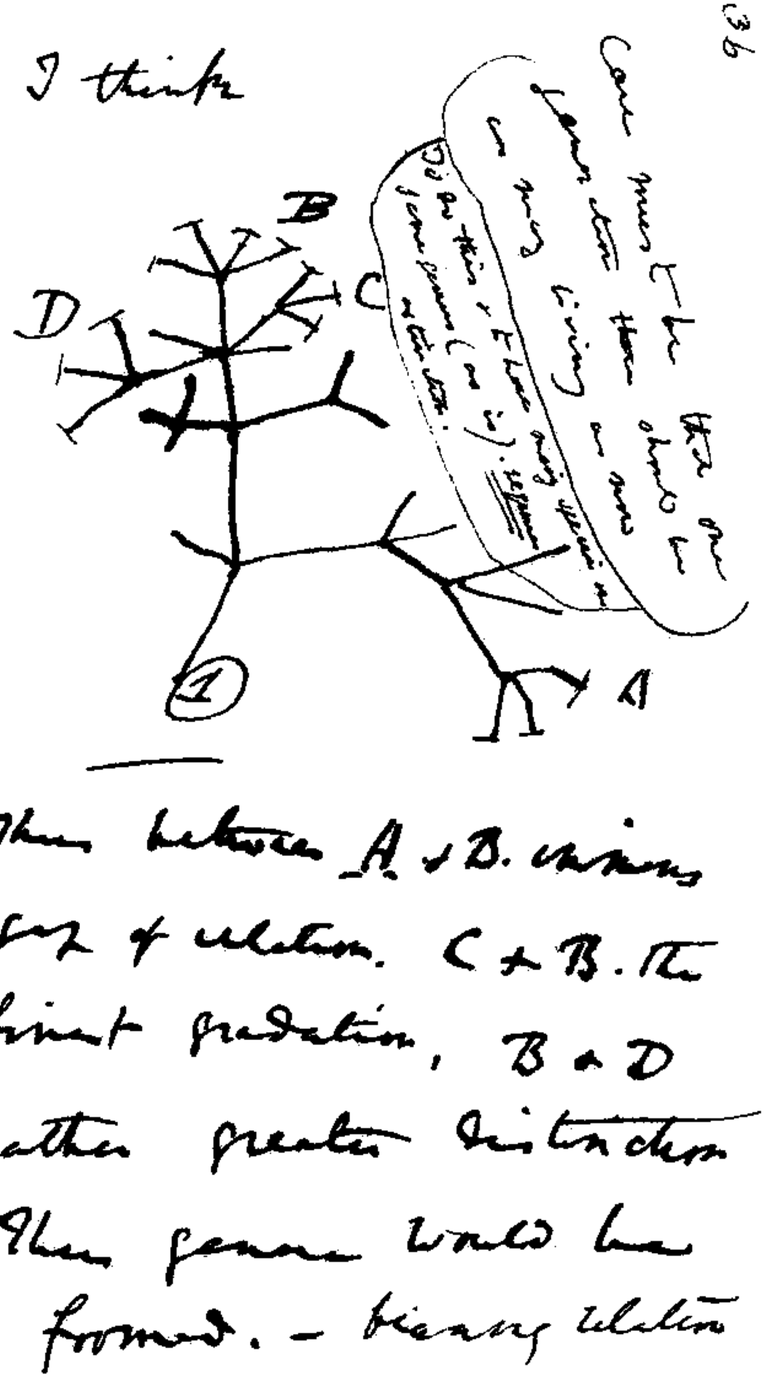
AI-Driven Discovery of QT Prolonging Drug-drug Interactions

Nicholas P. Tatonetti, PhD
Vice Chair and Associate Professor of Computational Biomedicine
Associate Director of Computational Oncology, Cedars-Sinai Cancer
Cedars-Sinai Medical Center
Los Angeles, CA
@nicktatonetti

Gold Lab Symposium 2023

All studies approved by Institutional IRBs

Funding support provided by NIH, Pfizer, Amgen, Janssen

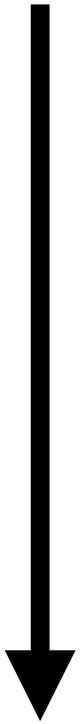


Observation is the starting point of biological discovery

- Charles Darwin observed relationship between geography and phenotype
- William McBride & Widukind Lenz observed association between thalidamide use and birth defects

The tools of observation are advancing

- Human senses
  - sight, touch, hearing, smell, taste
- Mechanical augmentation
  - binoculars, telescopes, microscopes, microphones
- Chemical and Biological augmentations
  - chemical screening, microarrays, high throughput sequencing technology

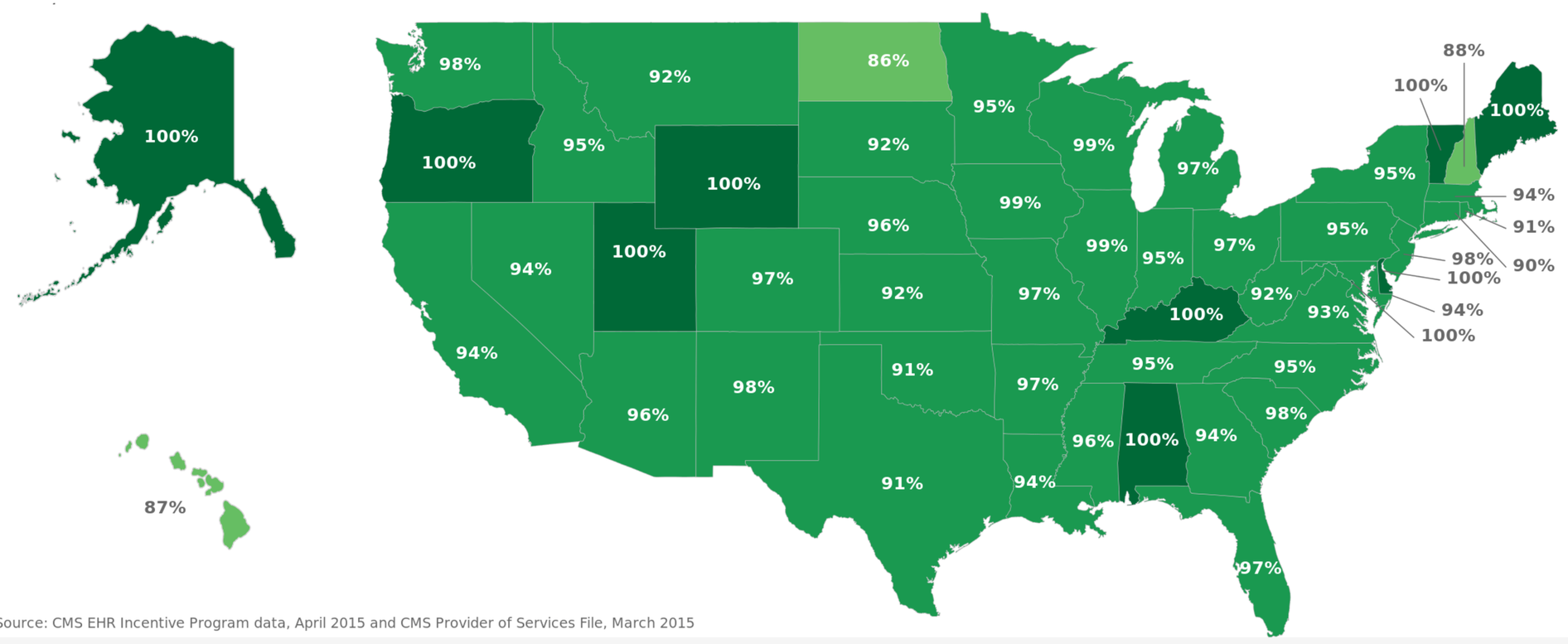


Bytes to KB

Megabytes to Terabytes

Your doctor is observing you like never before

>99% of Hospitals have Electronic Health Records

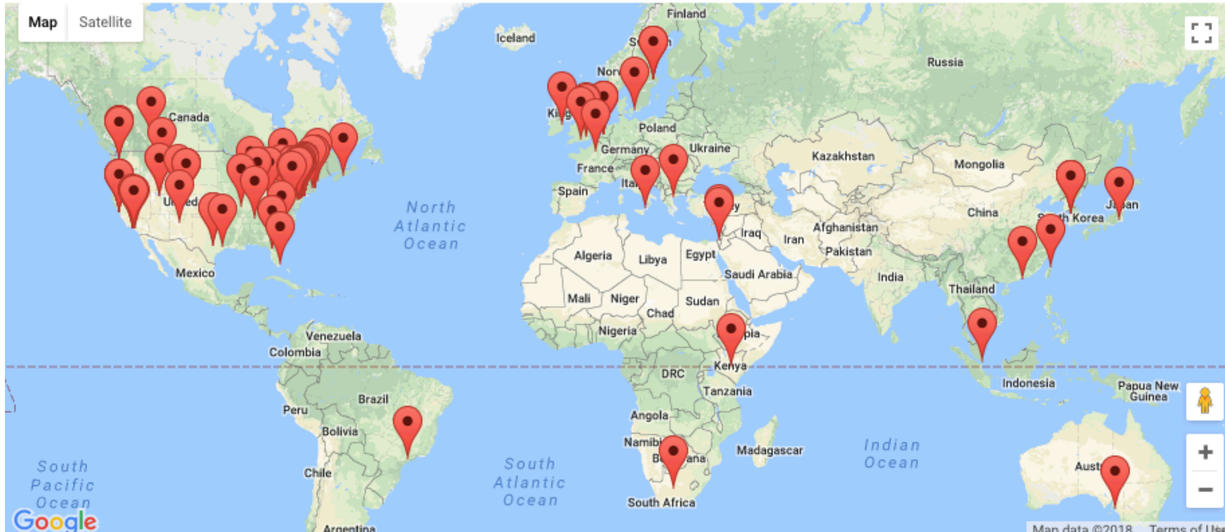


Source: CMS EHR Incentive Program data, April 2015 and CMS Provider of Services File, March 2015

OHDSI

OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

- Goal: 1 billion patient records in a common data model
- ~800 million patient records integrated
- Automated tools available



Observation analysis in a *peta*byte world

- Darwin, McBride, and Lenz were working with *kilo*bytes of data
- Today, we observing *tera*bytes and *peta*bytes of data everyone
- Data mining is about making the tools of data analysis (“hypothesis generation”) catch up to the tools of observation

But there’s a problem…

…behavior confounds observations

painting by Stable Diffusion v1.5

Every drug order is an experiment.

Every drug order is an experiment.

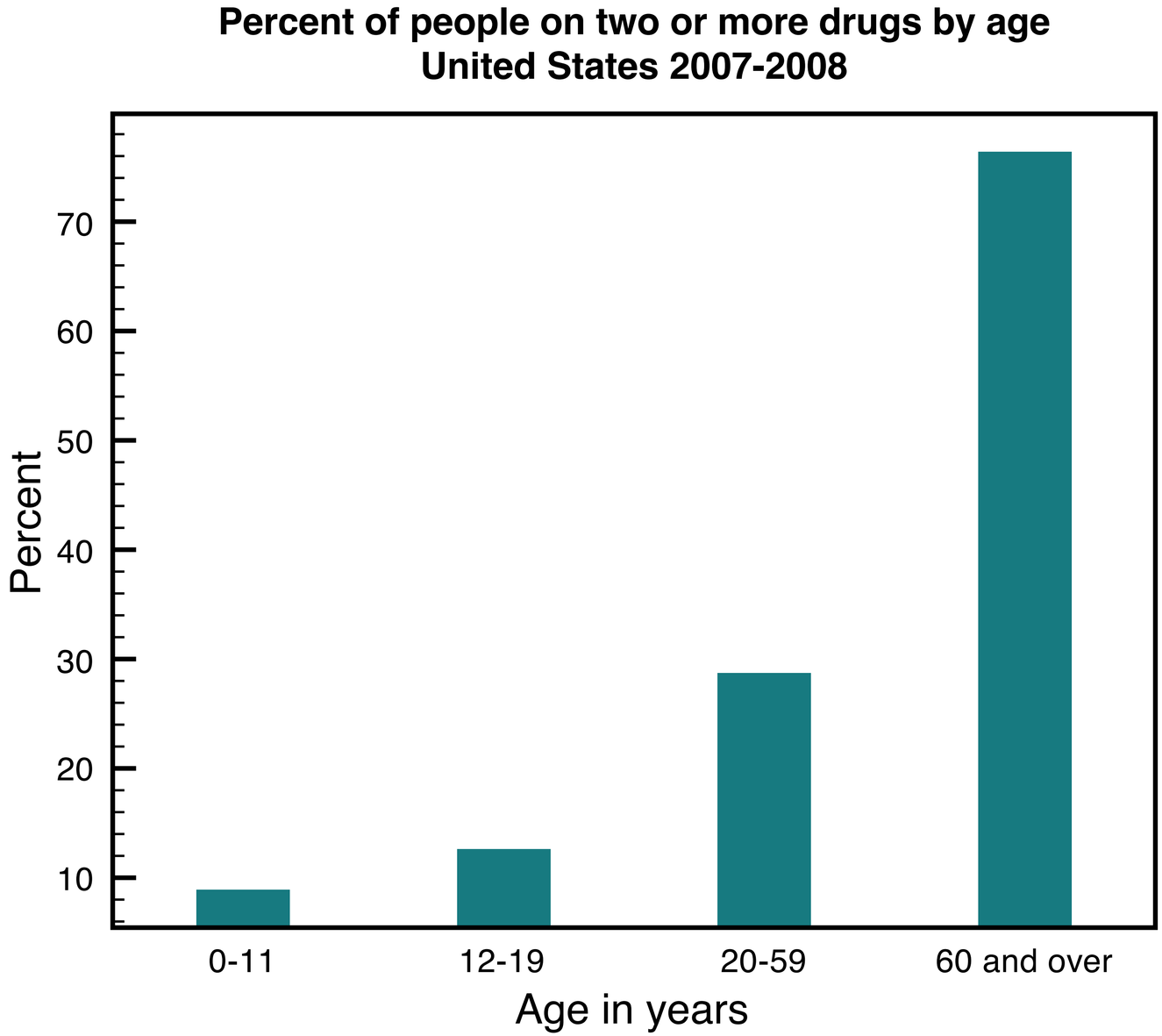
Can observational data be used to study hidden Drug-Drug Interactions?

Drug-drug interactions (DDIs)

- DDIs can occur when a patient takes 2 or more drugs
- DDIs cause unexpected side effects
  - 10-30% of adverse drug events are attributed to DDIs
- Understanding of DDIs
  - Improved safety as dangerous combos are avoided
  - reveals underlying human biological networks

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

- Clinical trials do not typically investigate drug-drug interactions
- **Observational studies** are the only systematic way to detect drug-drug interactions

Post-market Drug Safety Surveillance Systems

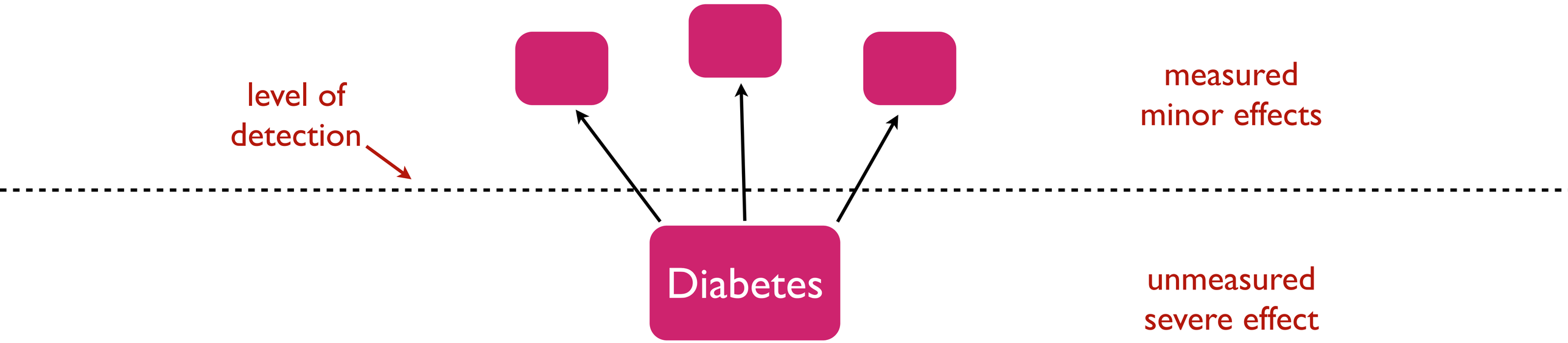
- Contain clinical data on millions of patients over many years
- Currently being used to establish single drug adverse events (pharmacovigilance)
- Eg. **Spontaneous Adverse Event Reporting Systems**
  - Collect adverse event reports for a patient (a snapshot in time)
  - Maintained by WHO > FDA > Health Canada

Drug-drug interactions are not reported

How to discover effects when they are not *directly* reported?

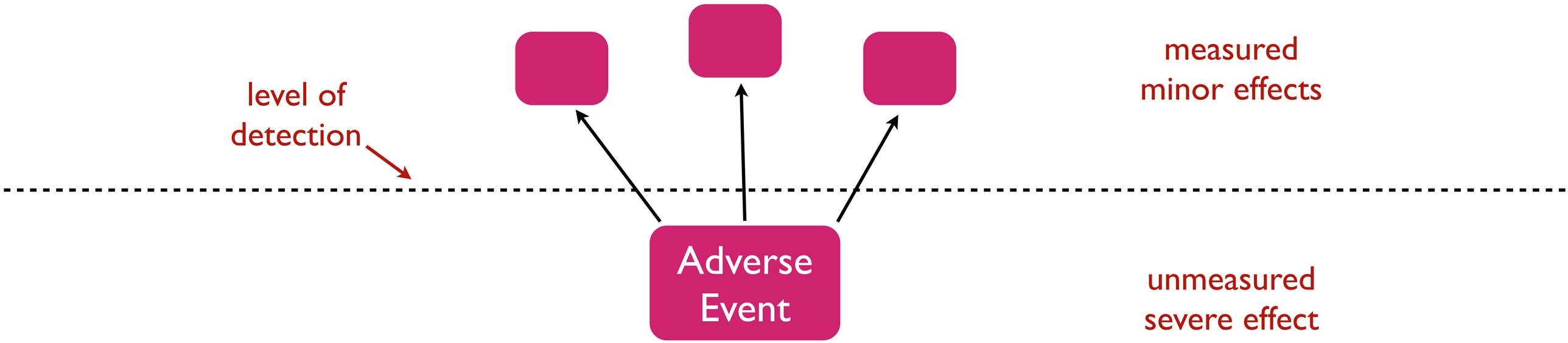
Diseases can be identified by the side effects they elicit

- 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

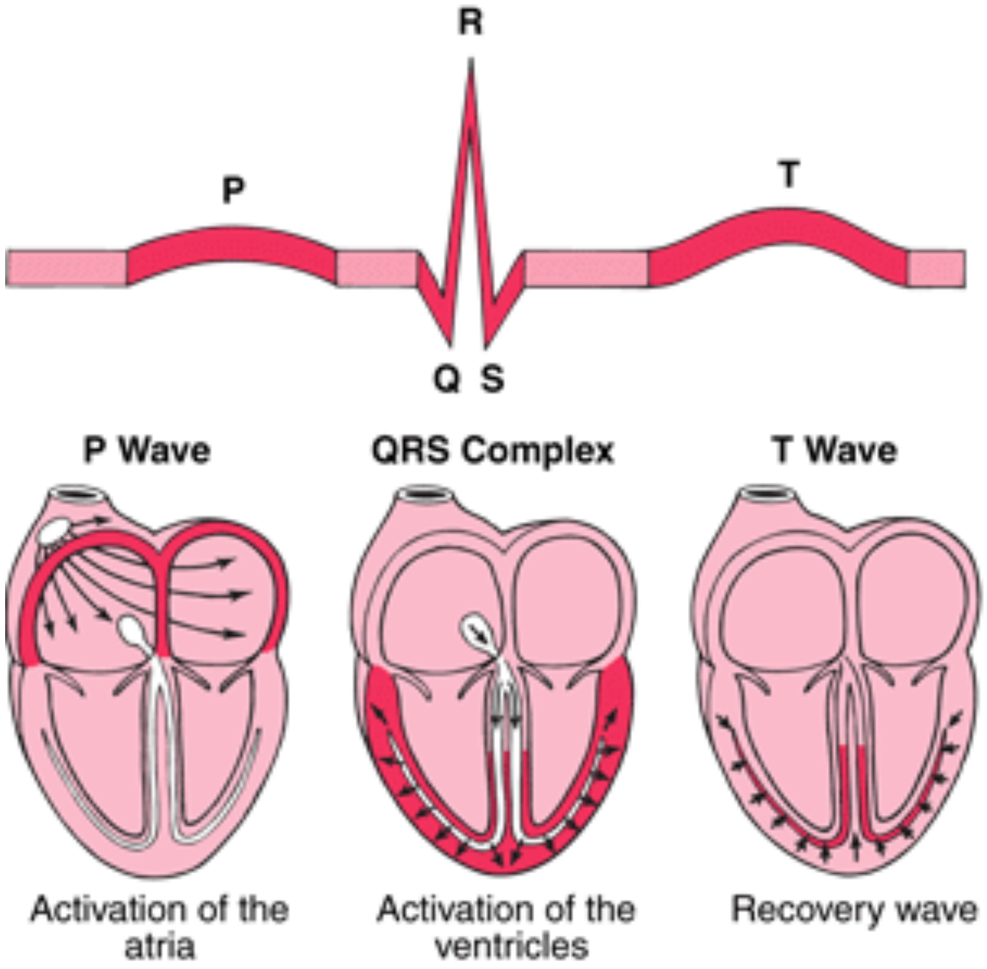


Severe ADE's can be identified by the presence of more minor (and more common) side effects

- Throw thousands of examples of known single-drug effects at an AI
- Let the AI learn the "signs and symptoms" of diagnosing an adverse drug reaction



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



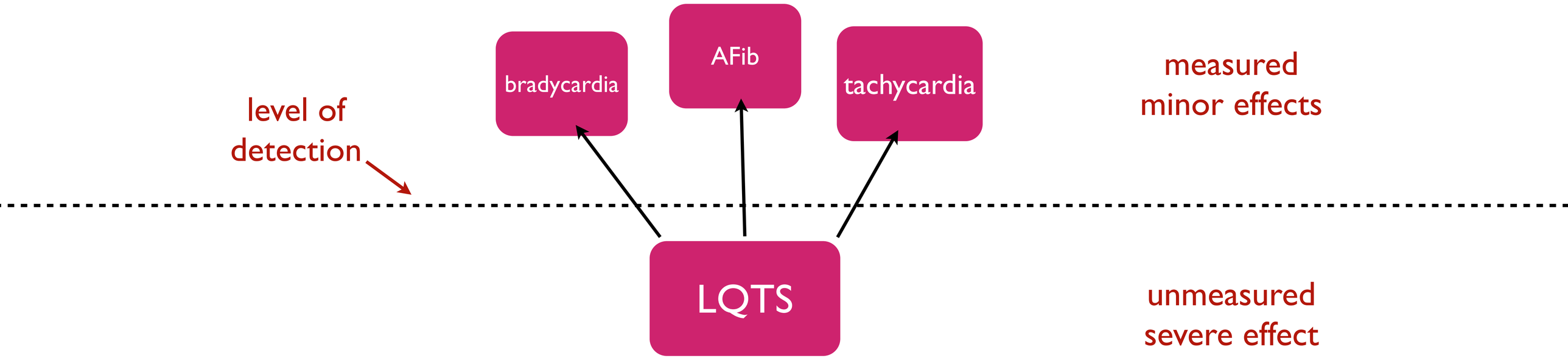
- Prolonging the QT interval can lead to a dangerous **ventricular tachycardia**
- Drugs can cause acquired LQTS by blocking the hERG channel
- We are good at testing for single drugs
- We know almost nothing when it comes to DDIs

E. Jason Wambsgans/Chicago Tribune

“The experiment began with thousands of patient files, millions of prescription orders, billions of clinical measurements and a single question: Could big data be used to discover deadly drug combinations

- Sam Roe and Karisa King

Identify acquired LQTS drug-drug interactions using Latent Signal Detection



Lorberbaum, et al. Drug Safety 2016

Latent Signal Detection of acquired LQTS

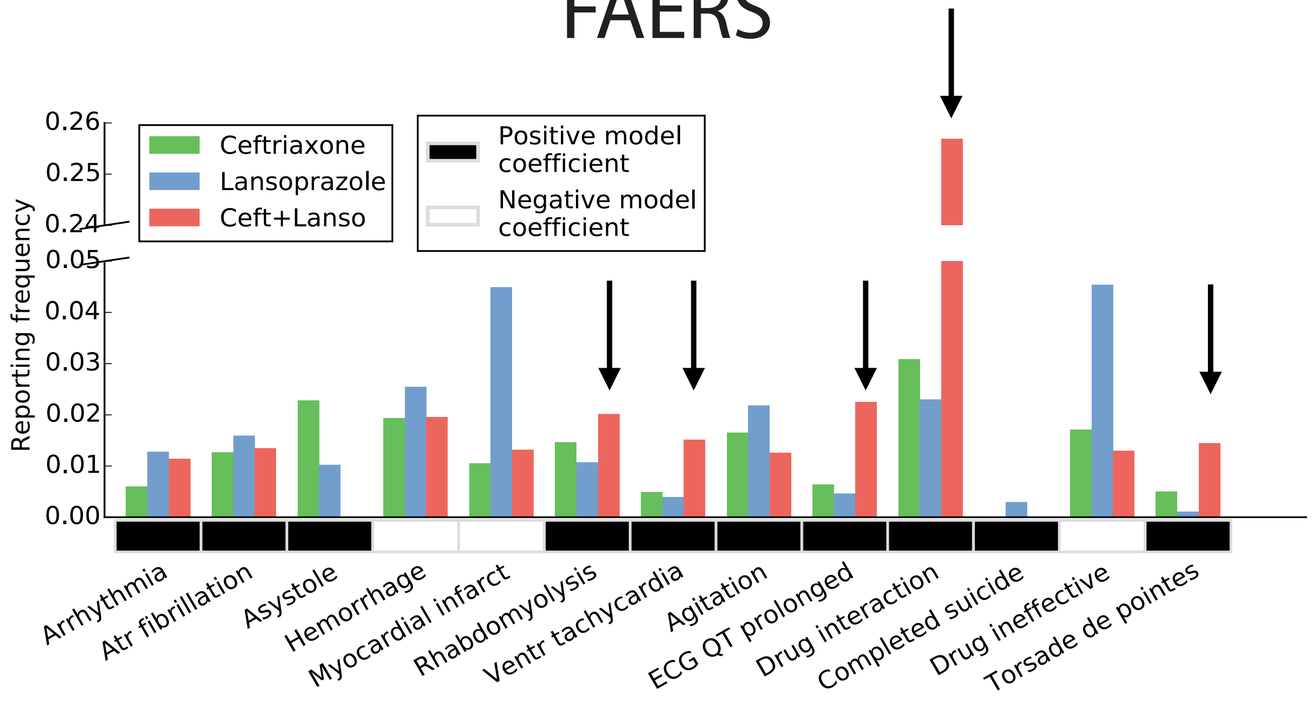
Top Prediction:
Ceftriaxone + Lansoprazole

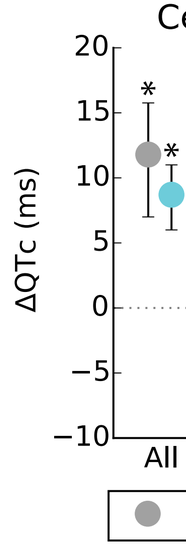
- *Ceftriaxone* — common in-patient cephalosporin antibiotic
- *Lansoprazole* — proton-pump inhibitor used to treat GERD, one of the most commonly taken drugs in the world

Lorberbaum, et al. Drug Safety (2016)
Lorberbaum, et al. JACC (2016)

FAERS

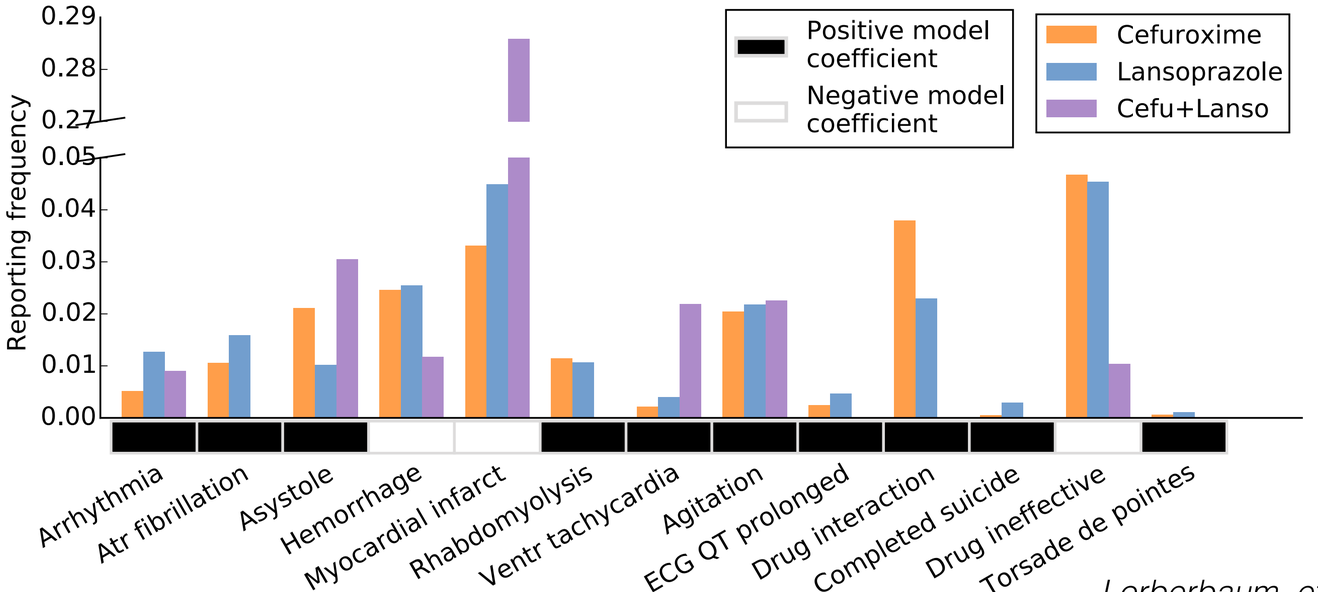
Ceftriaxone+ Lansoprazole

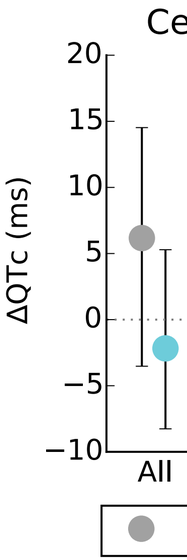




Side Effect Profile

Cefuroxime+ Lansoprazole

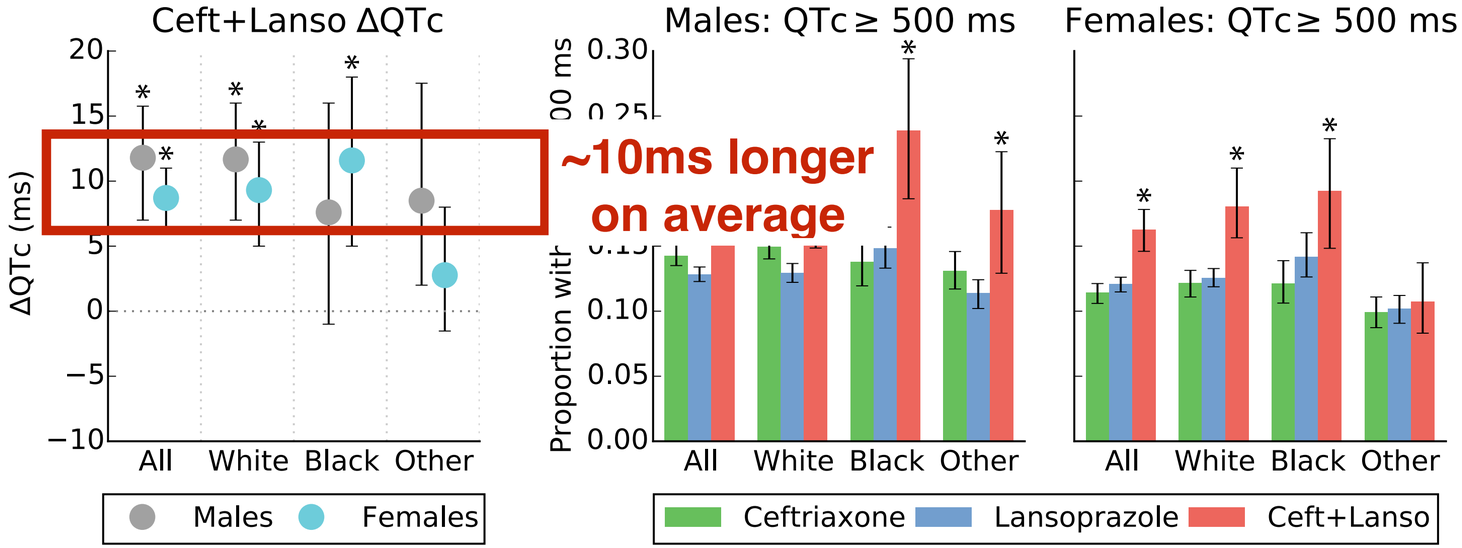




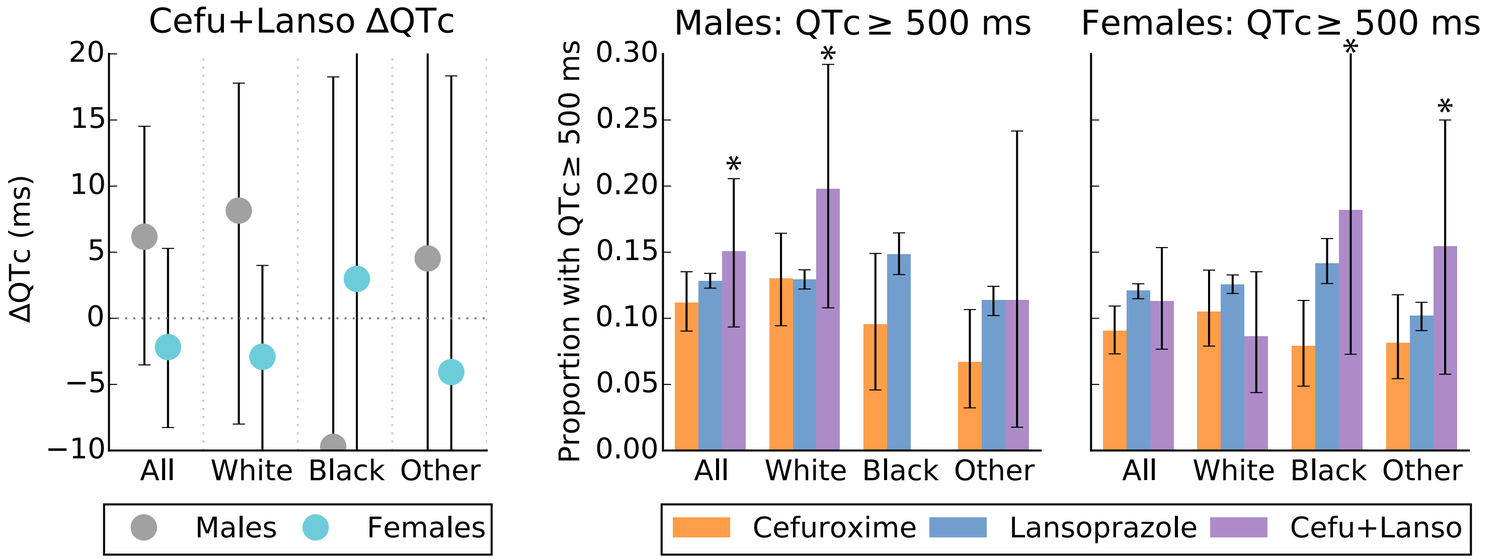
Lorberbaum, et al. JACC (2016)

Electronic Health Records

Ceftriaxone+ Lansoprazole



Cefuroxime+ Lansoprazole



Lorberbaum, et al. JACC (2016)

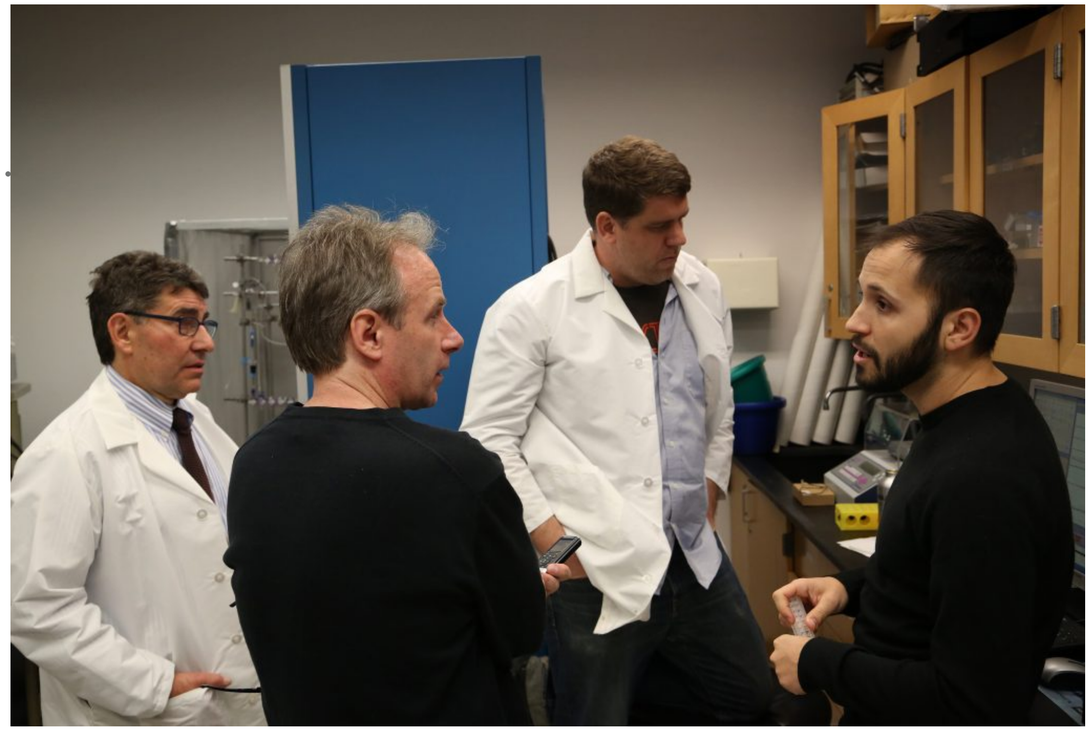
But there’s a problem…

…behavior confounds observations

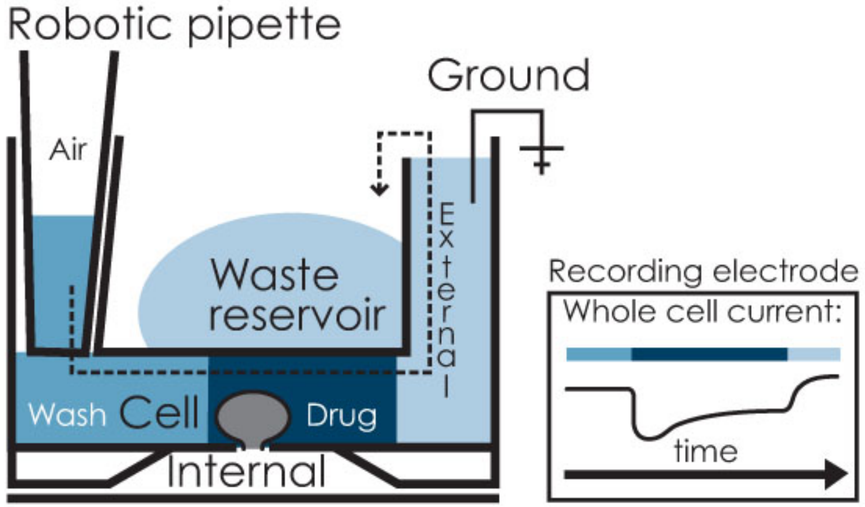
painting by Stable Diffusion v1.5

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

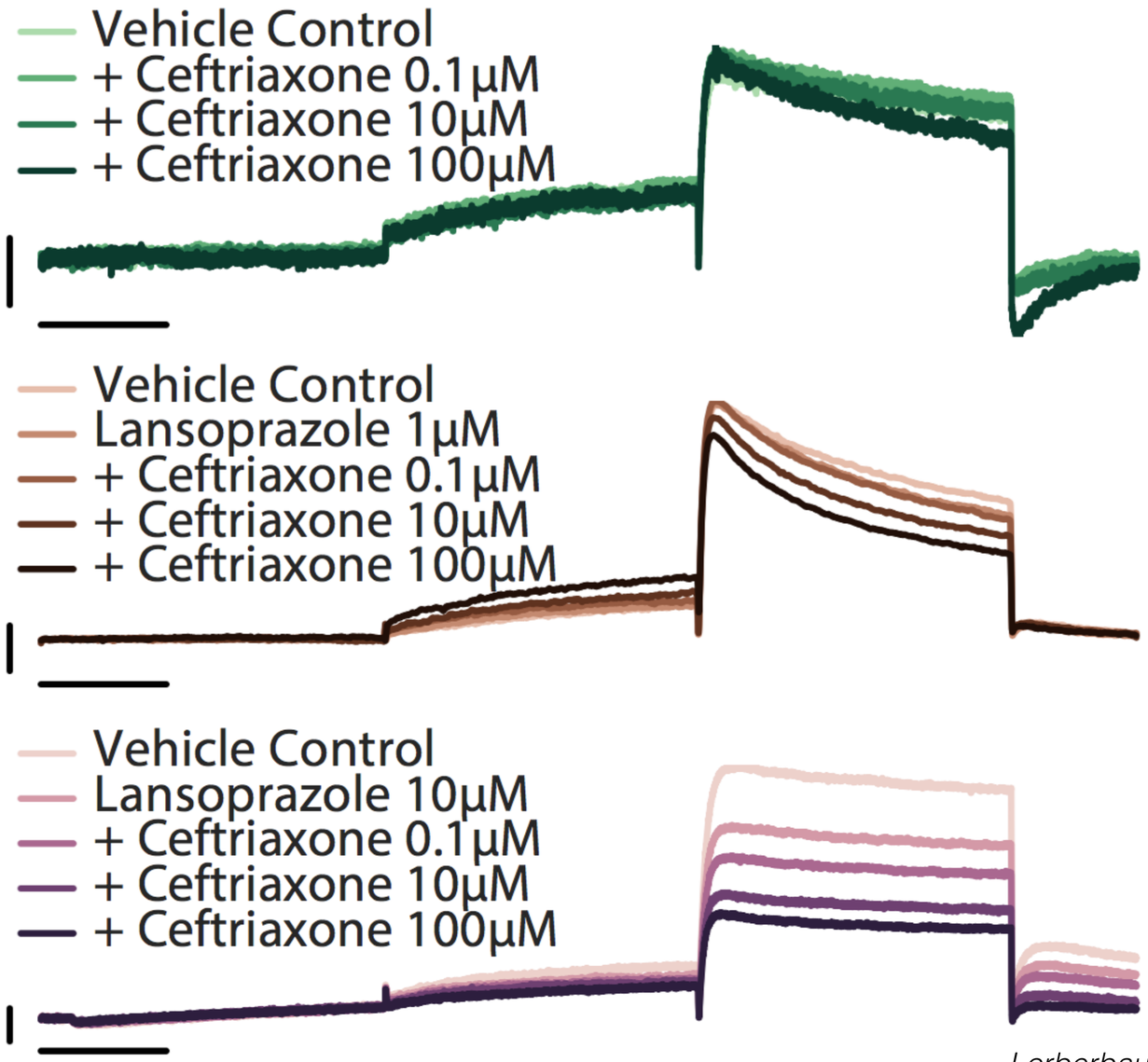


E. Jason Wambsgans/Chicago Tribune



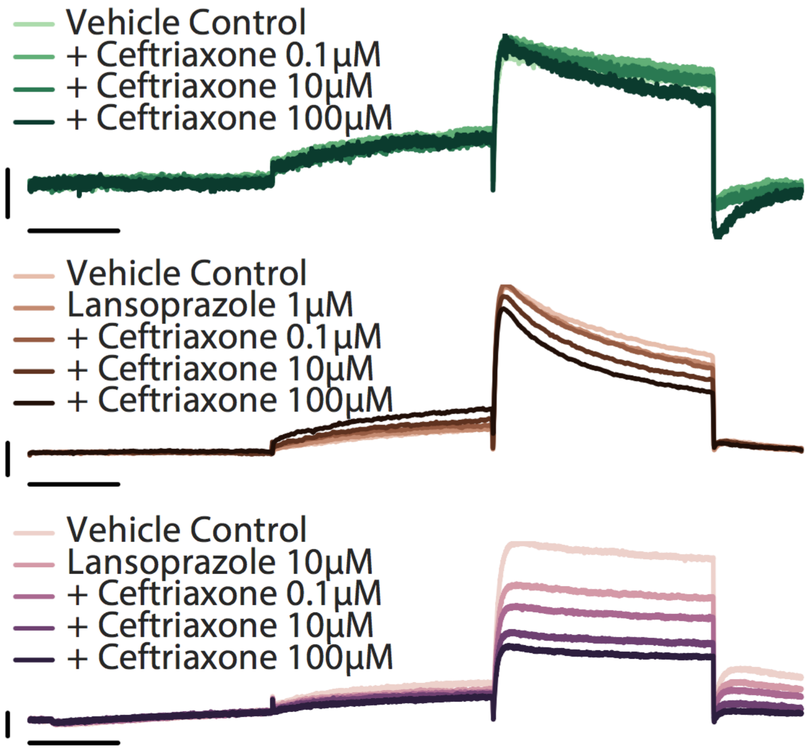
Nanion Patchliner

Ceftriaxone+Lansoprazole

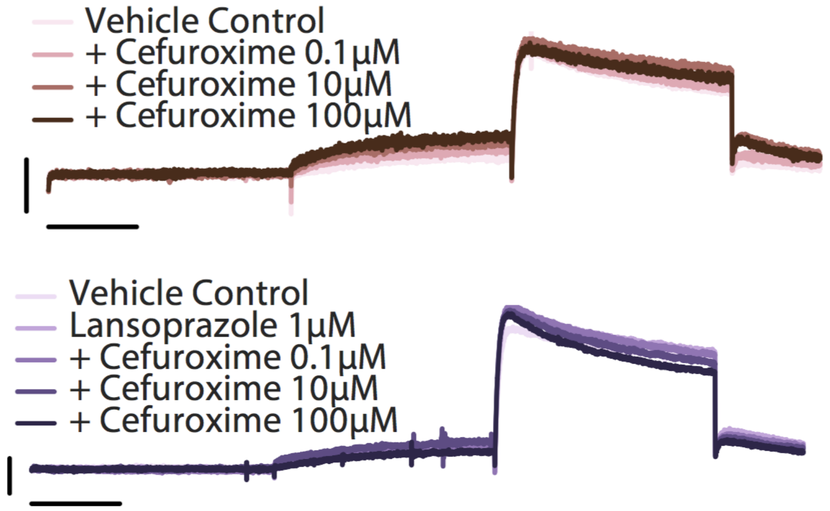


Lorberbaum, et al. JACC (2016)

Ceftriaxone+Lansoprazole

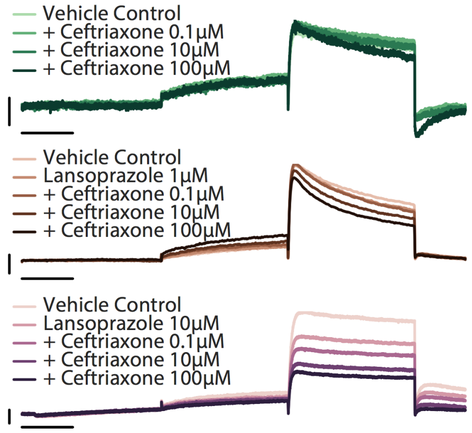


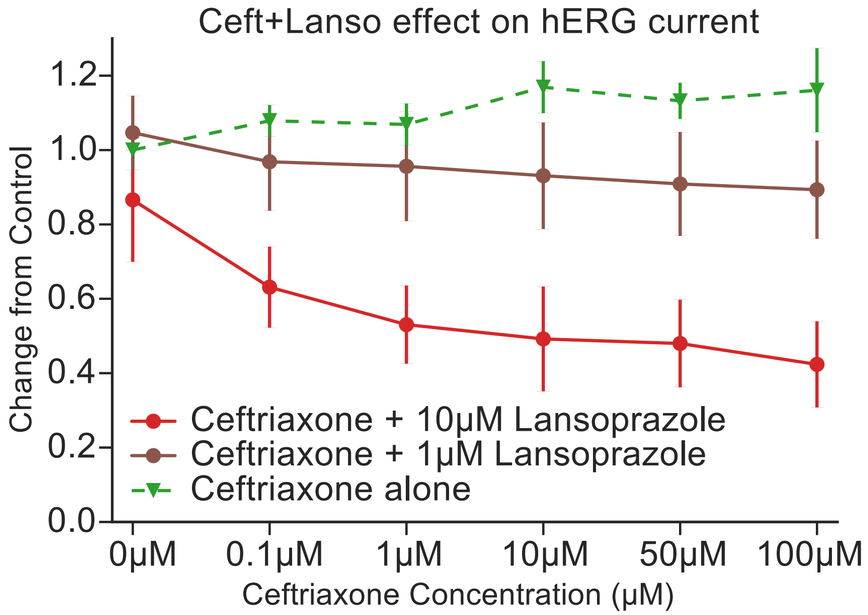
Cefuroxime+Lansoprazole



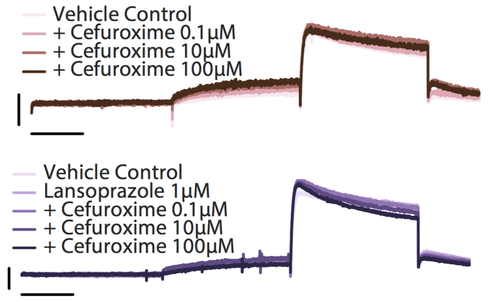
Lorberbaum, et al. JACC (2016)

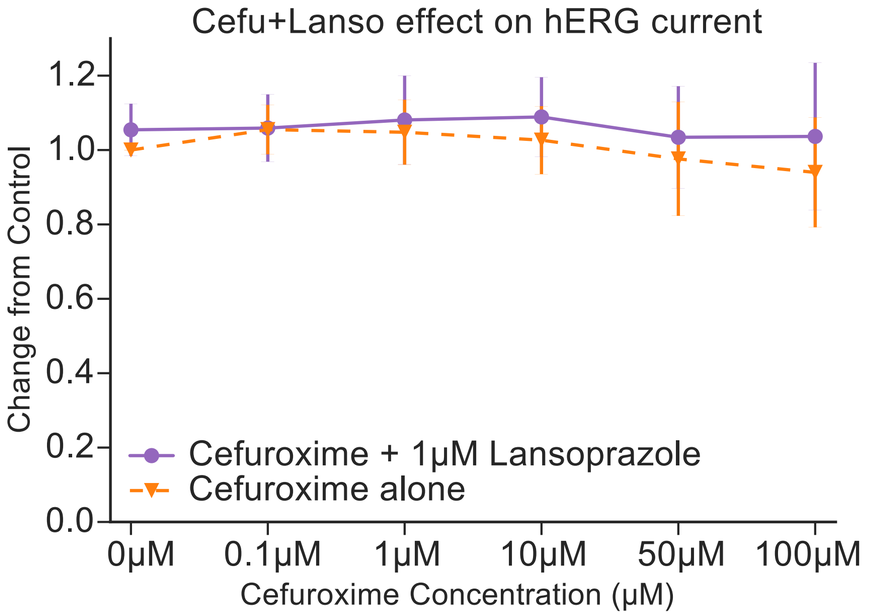
Ceftriaxone+Lansoprazole





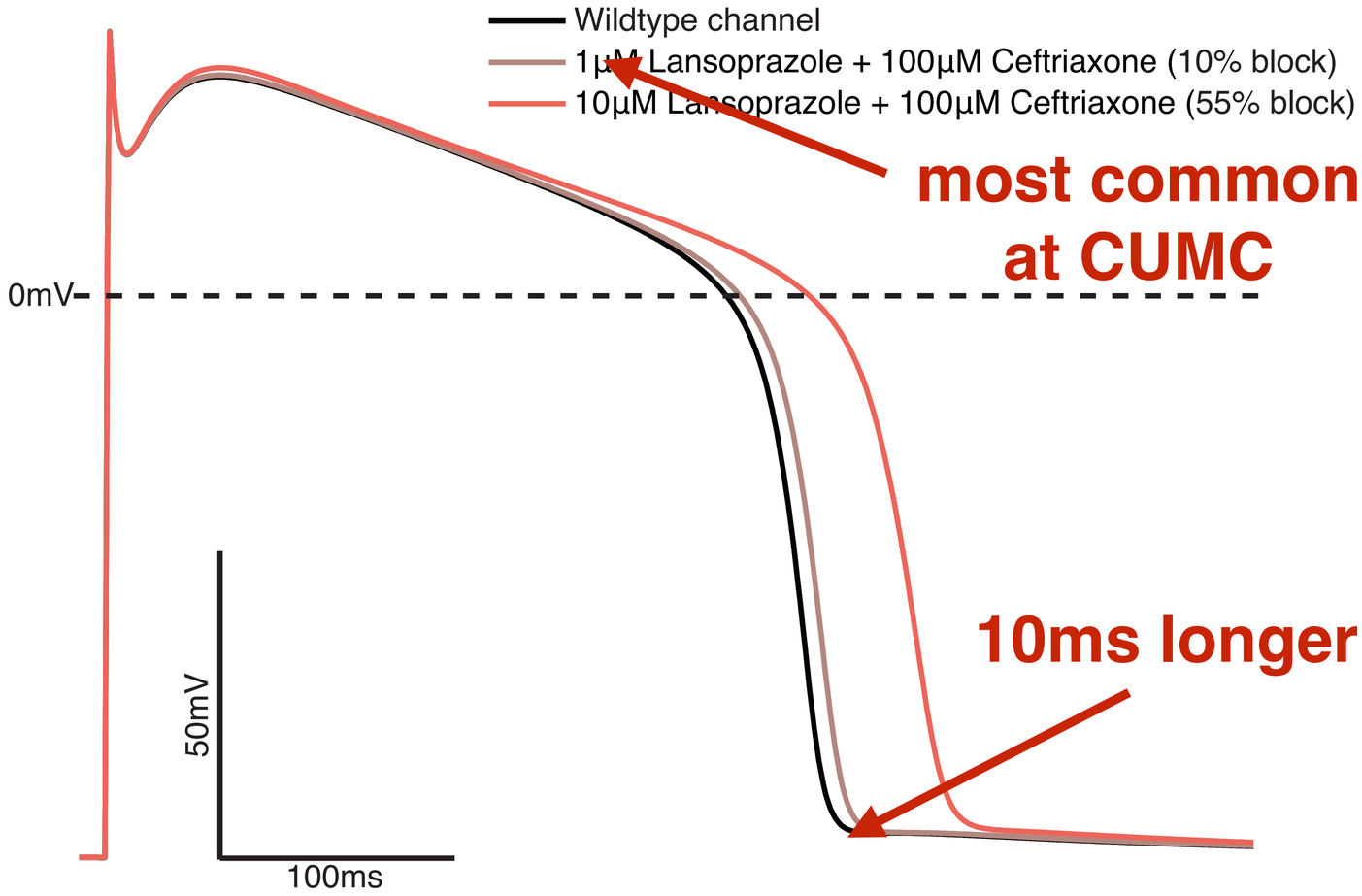
Cefuroxime+Lansoprazole





Lorberbaum, et al. JACC (2016)

Computational model of human ventricular myocyte



Lorberbaum, et al. JACC (2016)

Chicago Tribune

QUESTIONS? CALL 1-800-TRIBUNE THURSDAY, FEBRUARY 11, 2016 BREAKING NEWS AT CHICAGOTRIBUNE.COM

hone,
ar-old
by
bullet
Tragedy
violence

r in the Heart
ood, talking
father back
bullet came
ere to cut
mising life

lice would
eone was
firing at
took the
ive's life,
s killed
far this

to her
n the
truck
be a

hat's
ss is
vid
ise
for
"I
be
is
's

TRIBUNE WATCHDOG

E. JASON WAMBSGANS/CHICAGO TRIBUNE

Algorithms cover a glass wall at Columbia University in New York, where data scientist Nick Tatonetti, center, and his team used novel techniques in signal detection to identify potentially harmful drug interactions hidden in a vast database.

The hunt for dangerous doses

2017 Pulitzer Prize Finalist in Public Service

Thank you!

tatonettilab.org
@nicktatonetti
nicholas.tatonetti@cshs.org

Current Lab Members
Jiheum Park, PhD
Katie LaRow Brown, MA
Jenna Kefeli
Michael Zietz
Undina Gisladottir
Pietro Belloni
Jason Patterson
Yutaro Tanaka
Dhvani Mistry
Kevin Tsang
Apoorva Srinivasan
Jacob Berkowitz
Janie Weiss
Ben May

Collaborators
Jason Zucker, MD
Chin Hur, MD
Mitch Elkind, MD
Kenrick Cato, RN, PhD
Amanda Moy
Barry Fine, MD
Krzysztof Kiryluk, MD, MS
David Vawdrey, PhD
Ben Lebwhol, MD
Robert Kass, PhD
Kevin Sampson, PhD
Brent Stockwell, PhD
George Hripcsak, MD, MS
Suzanne Bakken, RN, PhD
David Goldstein, PhD
Ray Woosley, MD, PhD (Credible Meds)
Joel Dudley, PhD (Mount Sinai)
Li Li, PhD (Mount Sinai)
Patrick Ryan, PhD (OHDSI)
Russ Altman, MD, PhD (Stanford)

Funding
NIGMS R35GM131905
NIGMS R01GM107145
NCATS OT3TR002027
Herbert Irving Fellowship
PhRMA Research Starter
NCI P30CA013696
NIMH R03MH103957

Cedars Sinai

COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK