



Computational Drug Discovery

Marina Sirota, PhD
Assistant Professor

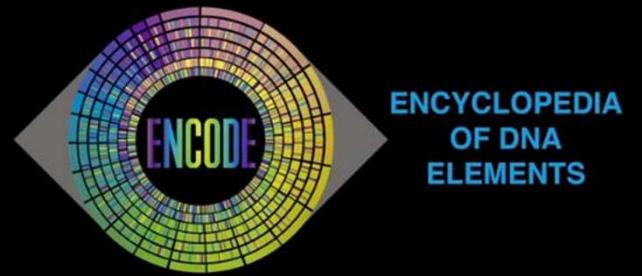
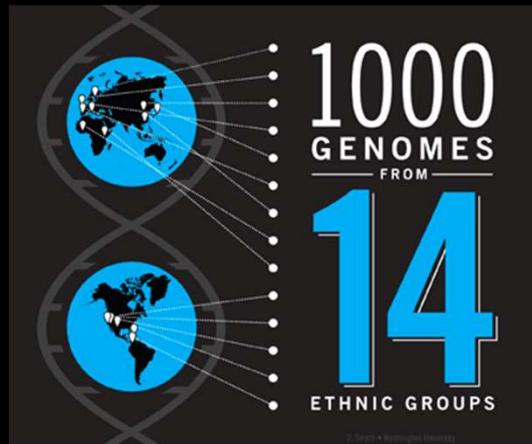


Sirota
Lab

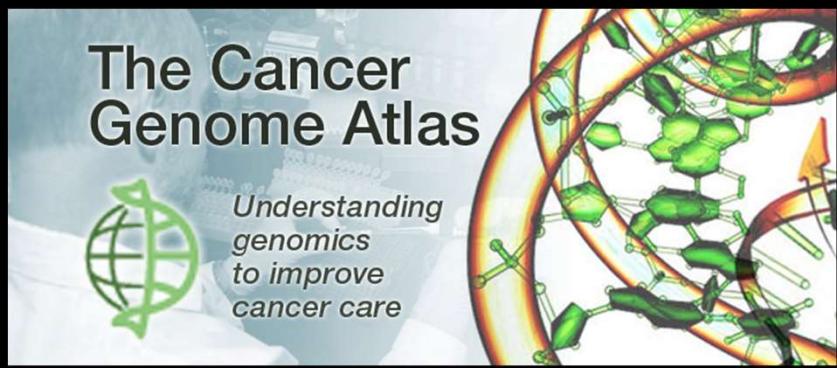


Bakar Computational Health
Sciences Institute

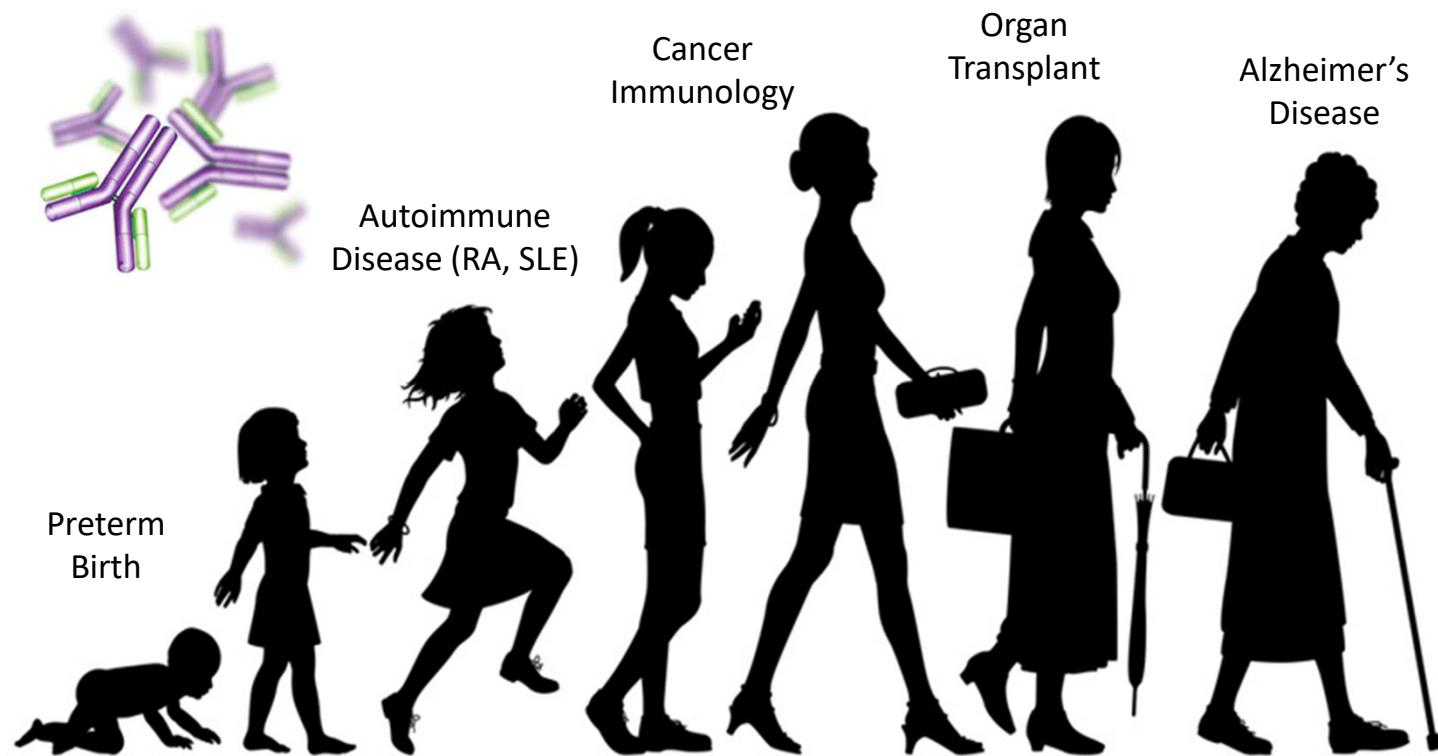
Why Now?



ExAC



Leveraging Computation to Understand Health and Disease Across the Lifespan...



Computational Drug Repurposing

- Target based drug repurposing
 - Genetics
- Disease based drug repurposing
 - Clinical data, molecular data
- Molecular modeling approaches
 - Docking-based drug repositioning
- Network approaches and global signature based approaches
 - “one drug – one target – one disease” is not sufficient for complex disease

Problem Statement

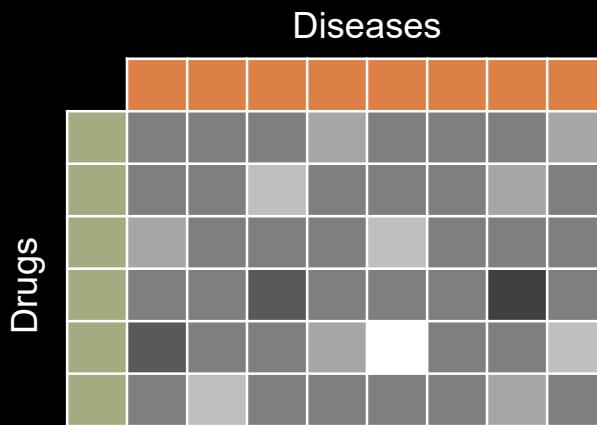
Can we use public data to systematically predict relationships between drugs and diseases?



Sirota M, Dudley JT, Kim J, Chiang AP, Morgan AA, Sweet-Cordero A, Sage J, Butte AJ. Discovery and Validation of Drug Indications Using Compendia of Public Gene Expression Data. *Science Translational Medicine*. Aug 2011.

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Data Sources



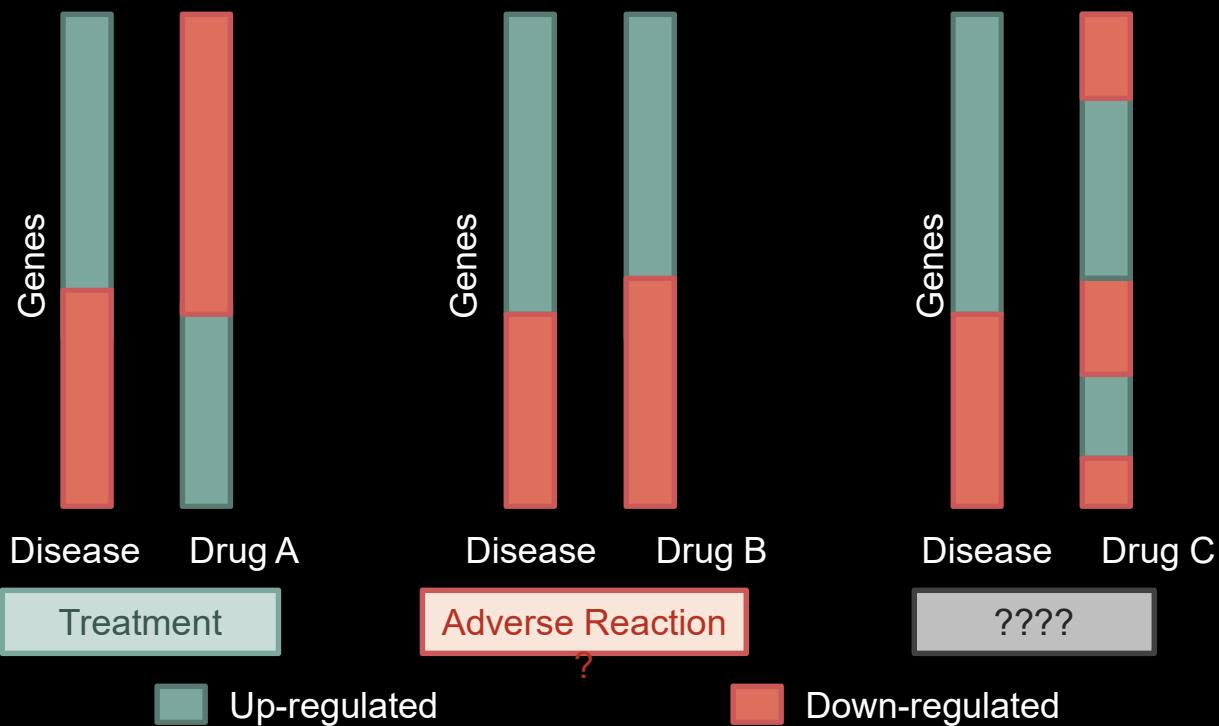
- Publicly available gene expression repository
 - Platforms – 17,214
 - Samples – 2,066,217
 - Series – 84,224
- There are numerous experiments dealing with disease
- Collection of expression data from cultured human cells
- Orig: 453 exprs of 164 drugs
- Now: 6,000 exprs, 1000+ drugs
- Covers broad range of effects
 - FDA approved drugs
 - Non drug bioactive small molecules

Barrett et al. NCBI GEO: archive for high-throughput functional genomic data. Nucleic Acids Res. 2009.

Lamb et al. The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease. Science. 2006.

Hypothesis

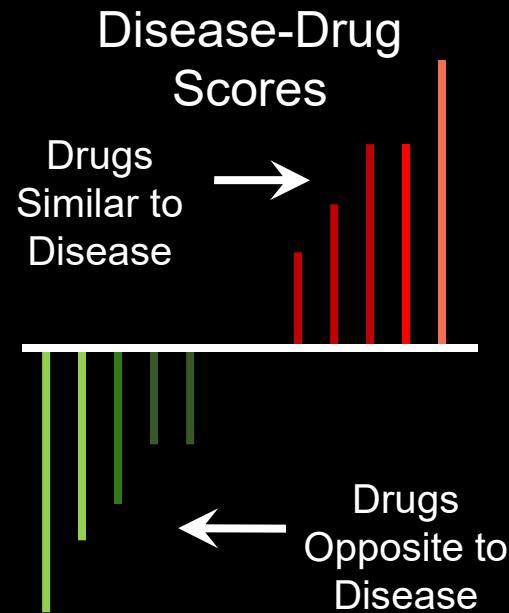
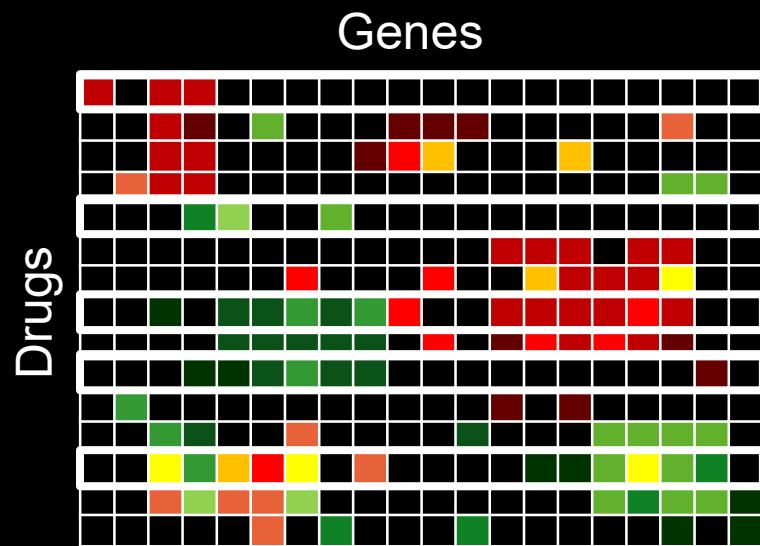
Gene Expression Profiles



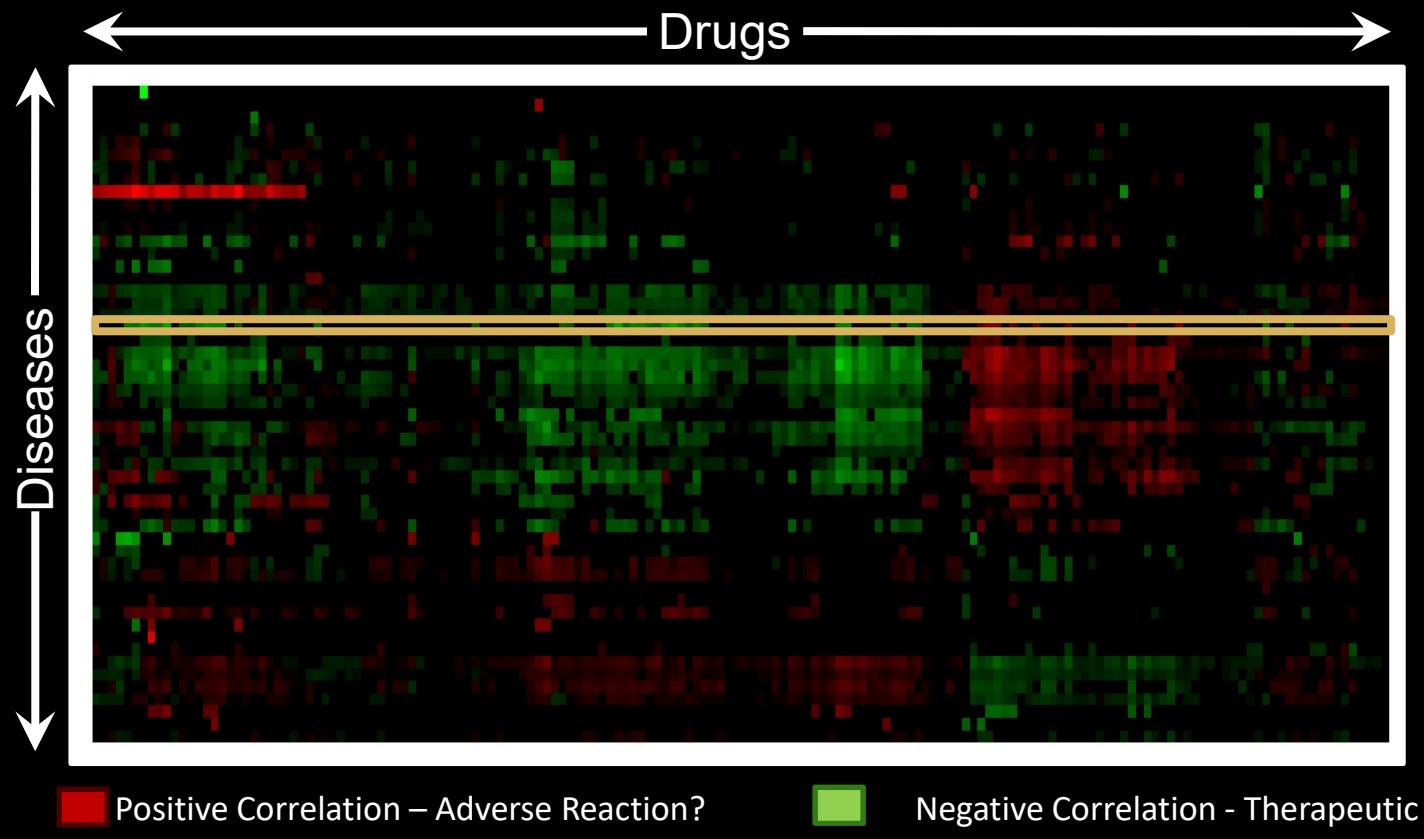
Lamb et al. The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease. Science. 2006.

Computational Pipeline

Disease Gene Expression Signature

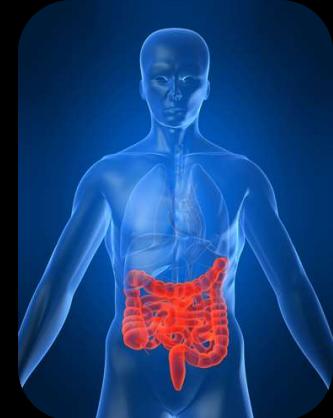


Drug-Disease Relationships

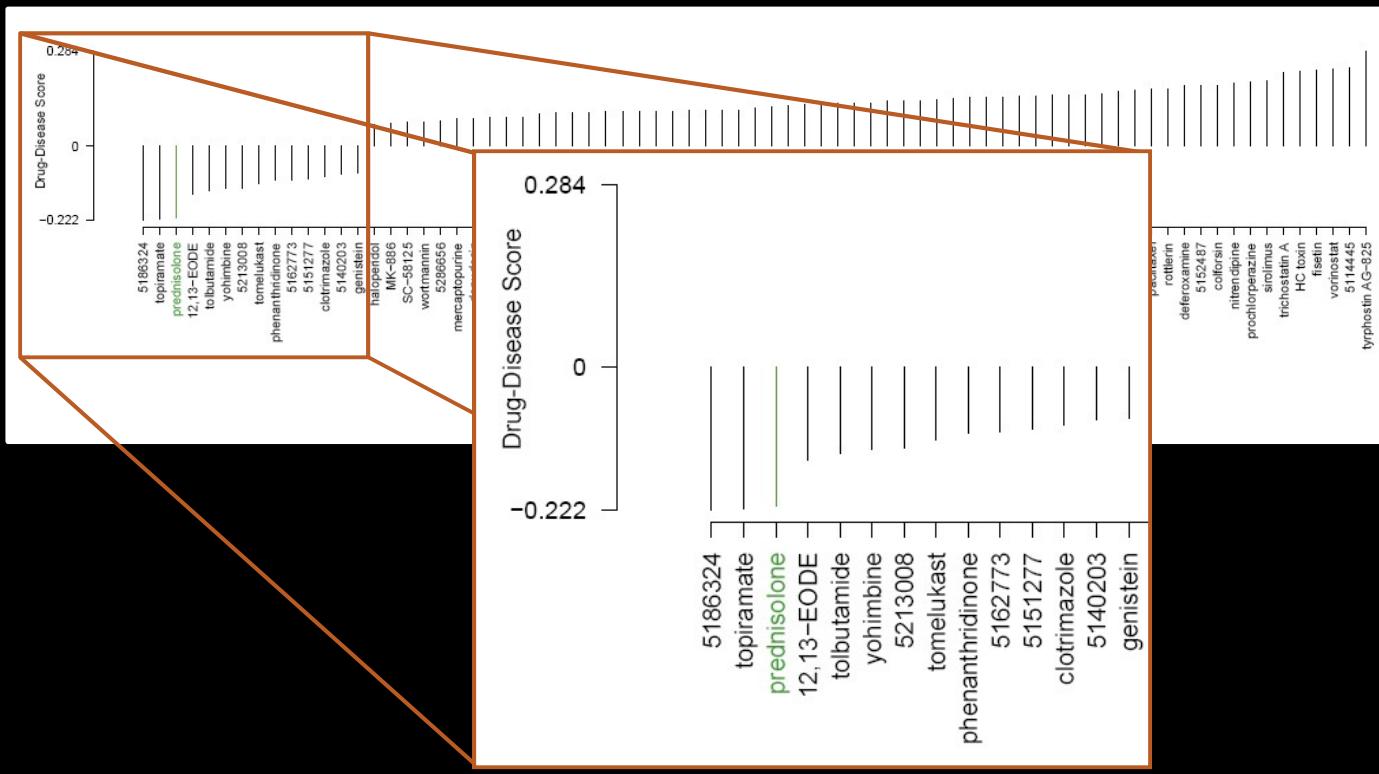


Crohn's Disease

- An inflammatory disease of the intestines that has an autoimmune component
- Affects 500,000 people in North America
- No known pharmaceutical cure
- Current solutions:
 - Reduce inflammation with anti-inflammatory drugs and corticosteroids (prednisone)
 - Bad side effects
 - Surgical solutions

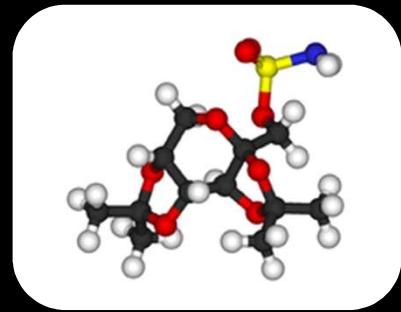


Therapeutic Predictions for Crohn's Disease

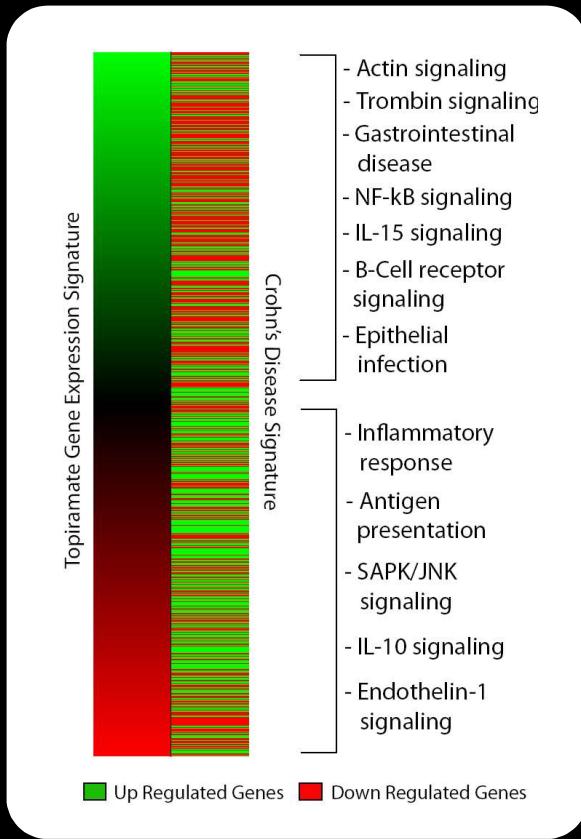


Topiramate – An Anti-Seizure Drug

- Suppresses the rapid and excessive firing of neurons that start a seizure
- Enhances GABA-activation
- Used to treat epilepsy, bipolar disorder
- Antidepressant
- Investigated as potential treatment for obesity and type II diabetes



Topiramate and Crohn's



Genes that are
up-regulated by the drug are
down-regulated in the disease

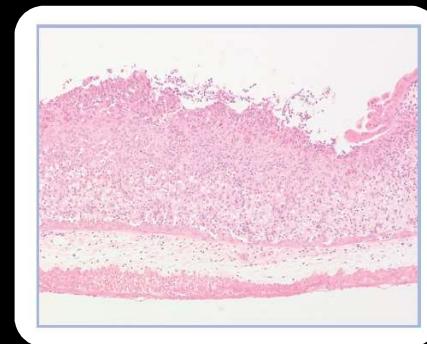
Genes that are
down-regulated by the drug are
up-regulated in the disease

Animal Model for Crohn's

- TNBS (trinitrobenzene sulfonic acid) + ethanol induced rats:
 - Excellent and reproducible experimental model for Inflammatory Bowel Disease (Crohn's and Ulcerative Colitis)



Normal



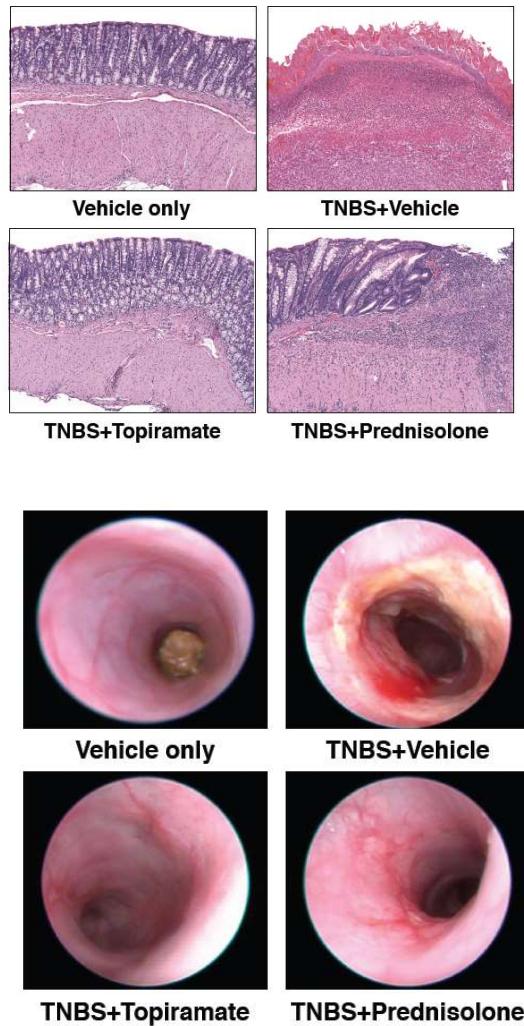
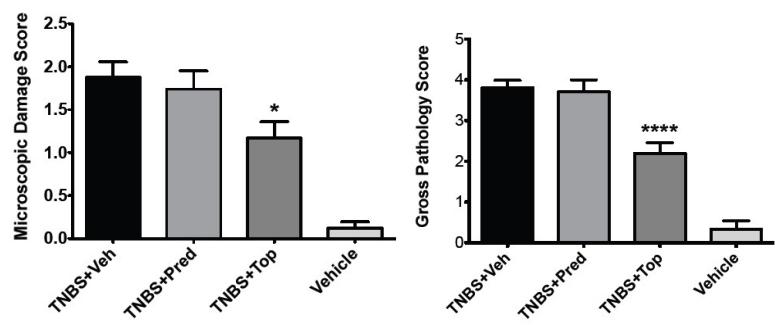
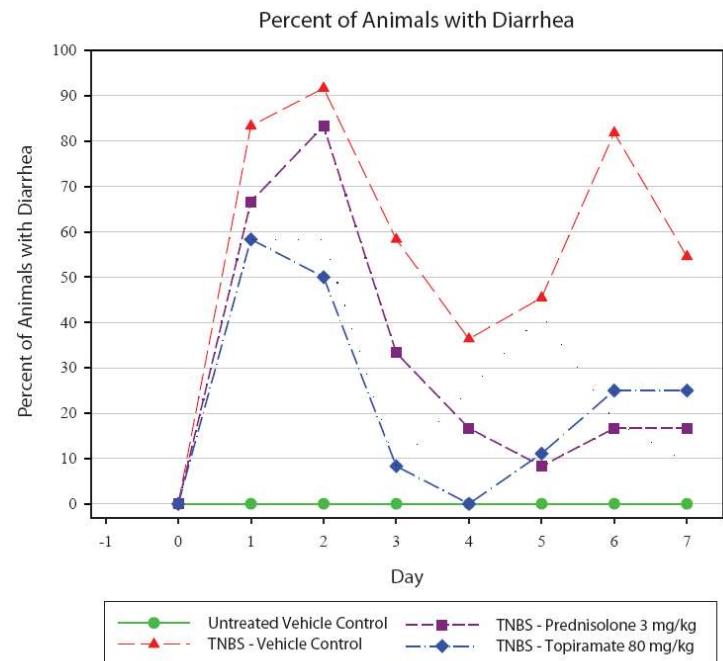
TNBS Induced

Two Follow-up Validation Studies

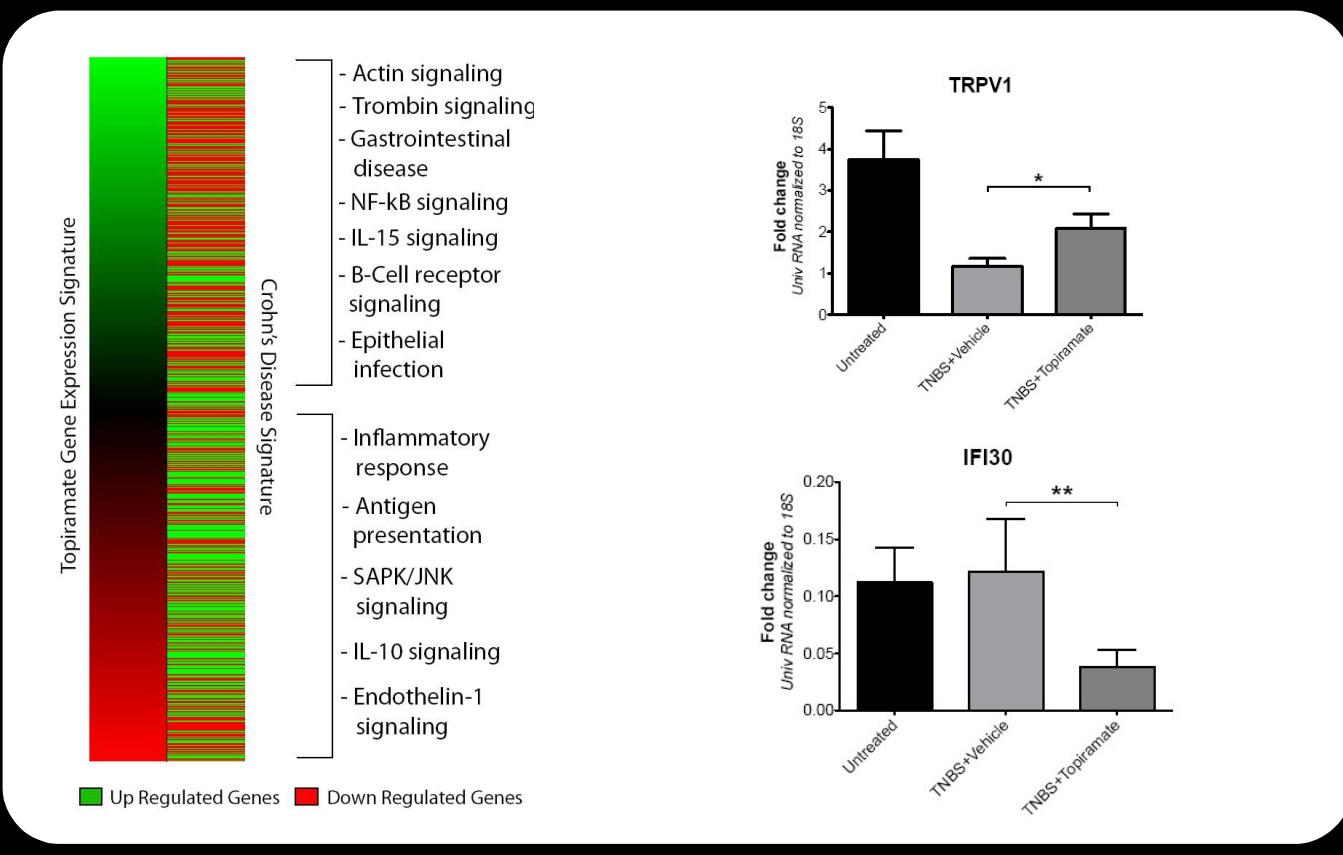
- 48 rats each – 4 groups of 12 rats
 - Healthy Controls
 - TNBS + Vehicle
 - TNBS + Prednisolone
 - TNBS + Topiramate
- 7 days
- Clinical Signs, Pathology Score, Histology
- Endoscopy Images



mdbiosciences

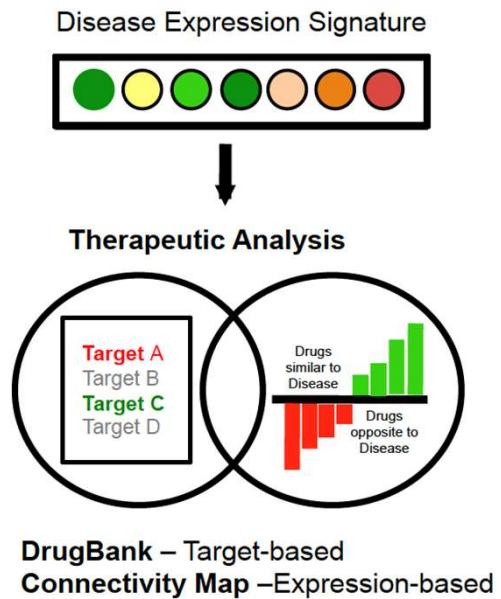


Drug-Disease Signature

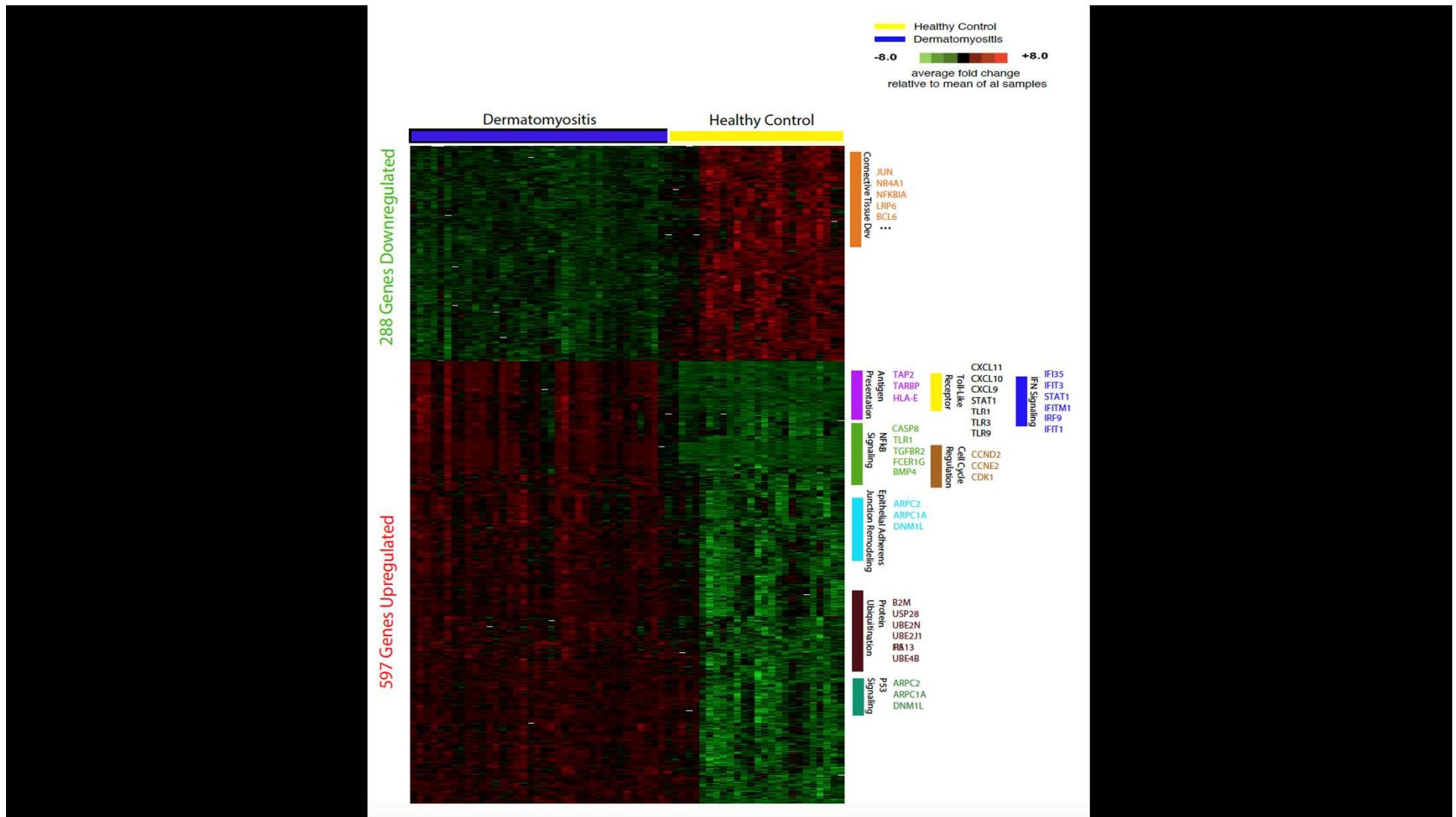


Application to Dermatomyositis

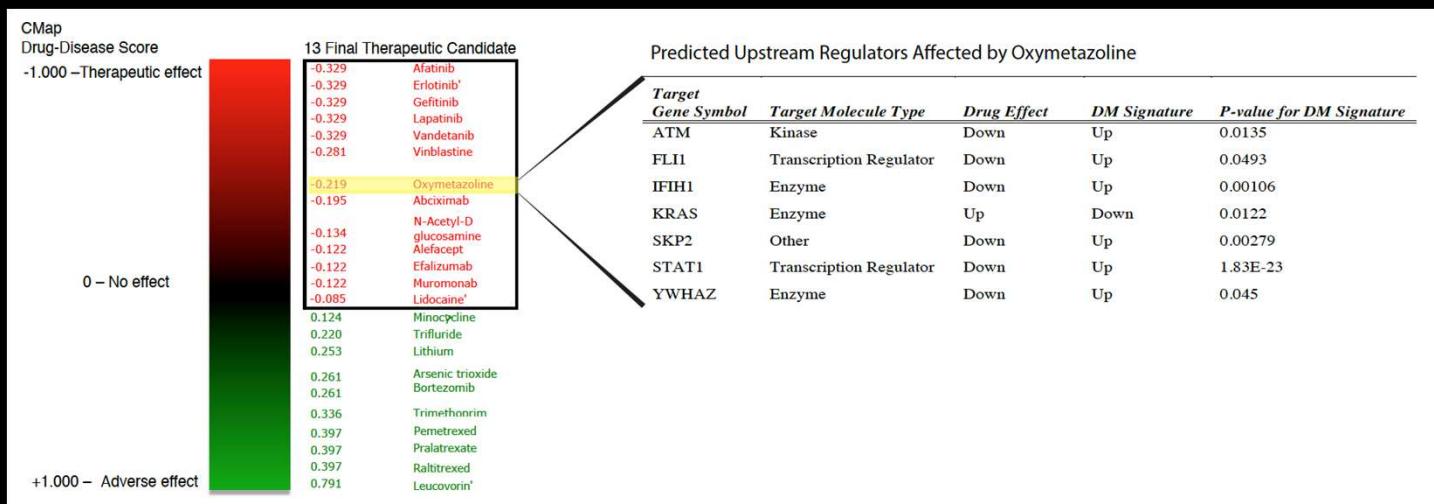
- Dermatomyositis (DM) is a systemic autoimmune disease affecting the skin
- Often painful and disfiguring and cause significant impairment in quality of life for patients
- Used a combination of a targeted and signature approach



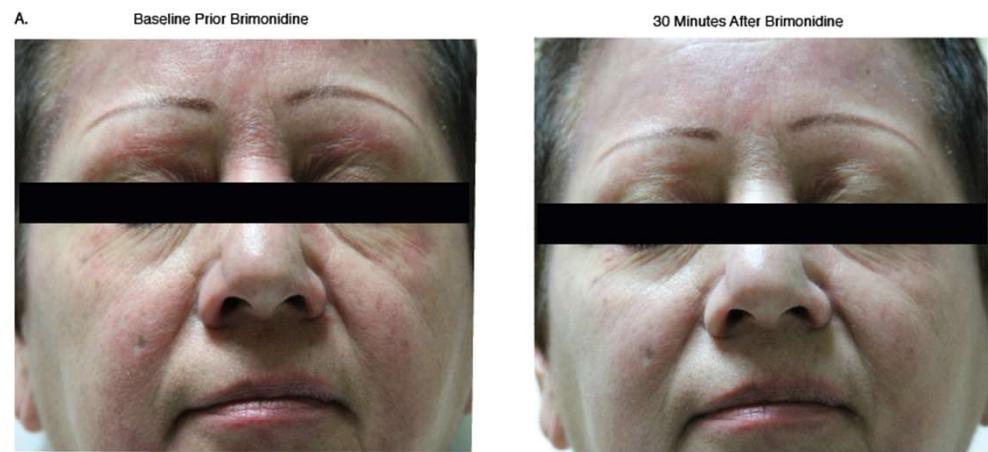
Cho HG, Fiorentino D, Lewis M, **Sirota M***, Sarin KY*. Identification of alpha-adrenergic agonists as potential therapeutic agents for dermatomyositis through drug-repurposing using public expression datasets. *J Invest Dermatol.* 2016 Mar 11. pii: S0022-202X(16)30867-3. doi: 10.1016/j.jid.2016.03.001.



Oxymetazoline for DM Treatment



- Selective alpha-1 agonist and partial alpha-2 agonist
- Good safety profile for topical forms for rosacea
- Brimonidine, another member of the alpha-2 agonist class available as a gel was tested in the clinic



RESEARCH ARTICLE

DRUG DISCOVERY

Discovery and Preclinical Validation of Drug Indications Using Compendia of Public Gene Expression Data

Mari
Aleja
Publish

RESEARCH ARTICLE

DRUG DISCOVERY

Computational Topiramate

Joel T. Dudley,^{1,2,3*} N
Silke Roedder,^{1,3} Ann
Pankaj Jay Pasricha,⁴

Identification of Alpha-Adrenergic Agonists

as Potent
Dermato
Using Pu

Hyunje Grace Cho BA
MD, PhD^{2, 4}✉

¹ School of Med

² Department o

³ Institute for C
California, US

JCI INSIGHT

RESEARCH ARTICLE

Combined inhibition of atypical PKC and



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ARTICLE

Received 7 Dec 2016 | Accepted 17 May 2017 | Published 12 Jul 2017

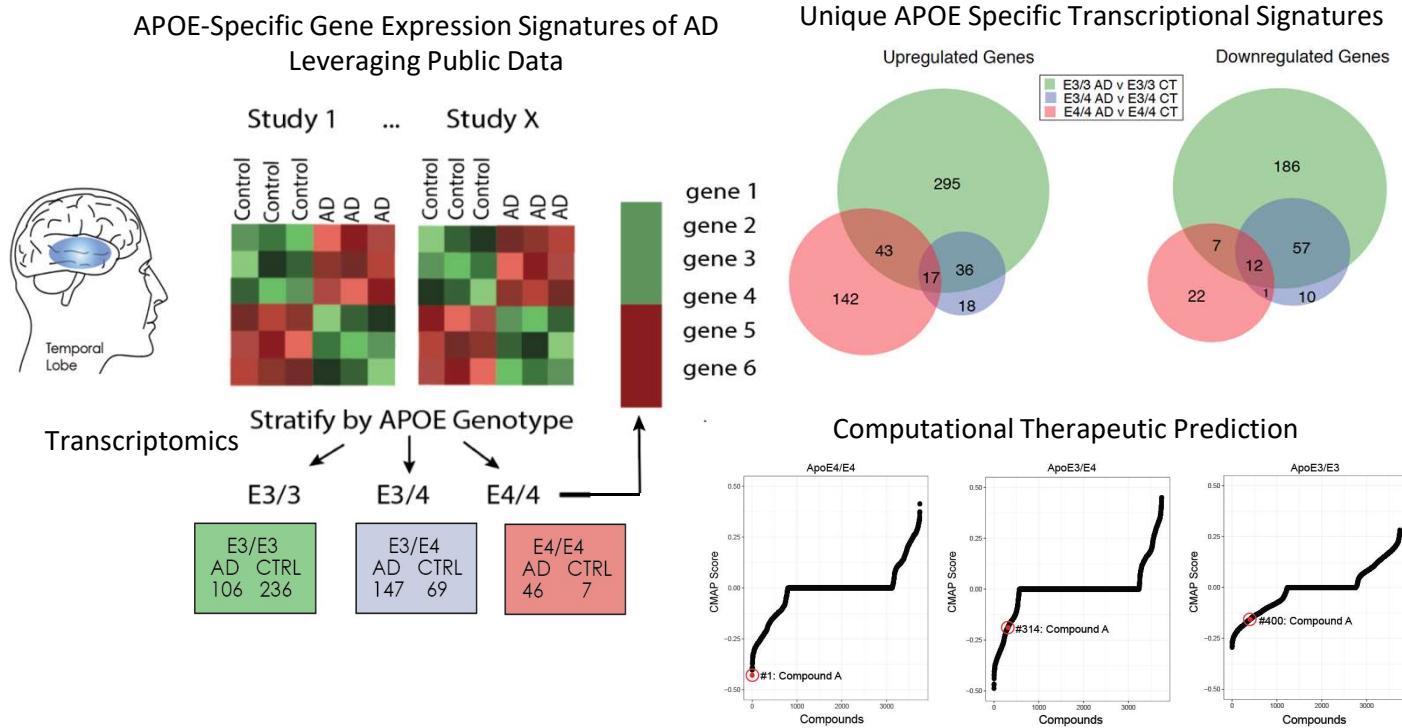
DOI: 10.1038/ncomms16022

OPEN

Reversal of cancer gene expression correlates
with drug efficacy and reveals therapeutic targets

Bin Chen^{1,*}, Li Ma^{2,*}, Hyojung Paik^{1,3}, Marina Sirota¹, Wei Wei², Mei-Sze Chu², Samuel So² & Atul J. Butte¹

Precision Medicine Approach to Drug Repurposing: Alzheimer's Disease



R01AG060393, R01AG057683

Ali Taubes, Yadong Huang, Under Review.

UCSF Electronic Medical Records (EMR)

- Time span: 2012 – today
- Number of patients: 922,59
- Data included:
 - Allergies
 - Diagnosis
 - Encounters
 - Immunizations
 - Lab tests
 - Medications orders
 - Procedure orders
 - Vitals
 - Imaging

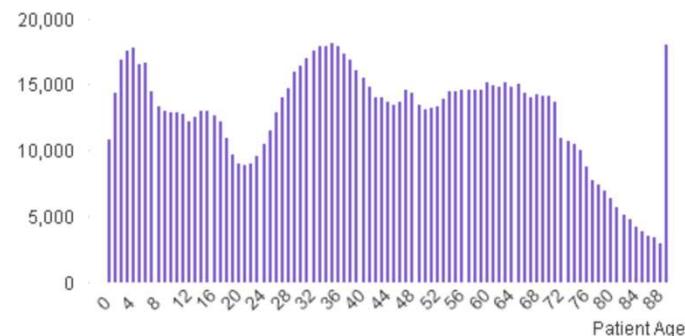


Deidentified patient data

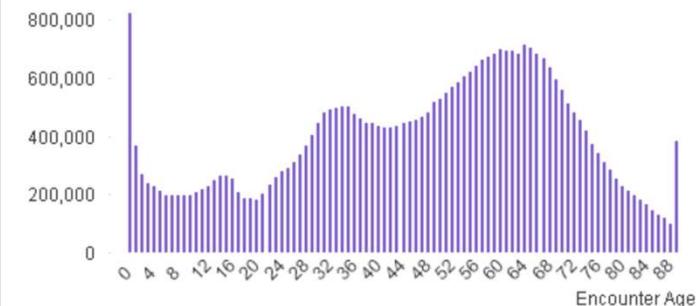
Patients 1,163,581 (100.0%)

Full View Top View

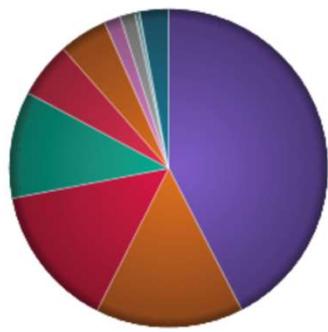
Patient Ages (current)



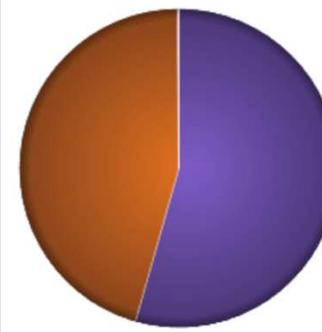
Patient Ages as of Encounter (count of encounters)



Race



Sex





University of California Research eXchange

SEARCH 12 MILLION PATIENT RECORDS

- ✓ The UC ReX Data Explorer enables search of 12 million de-identified patient records from the 5 UC medical centers with one query
- ✓ Complete NIH targeted Enrollment Tables by providing counts of eligible patients by gender, race and ethnicity
- ✓ Increase cohort identification for the study of rare diseases
- ✓ Expand your study from a single to a multi-site proposal
- ✓ Obtain coordinated data provisioning support through UC ReX

UC HEALTH

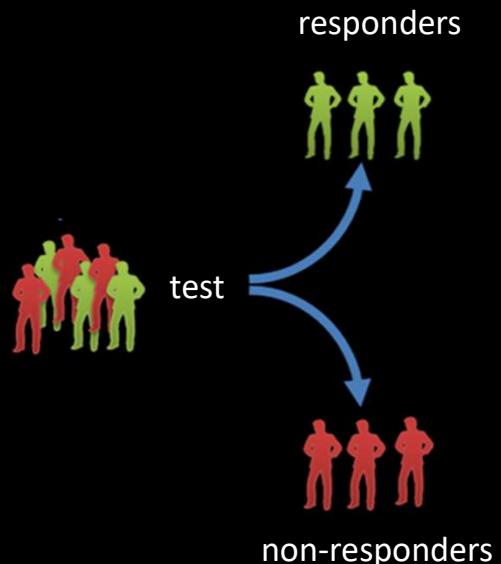
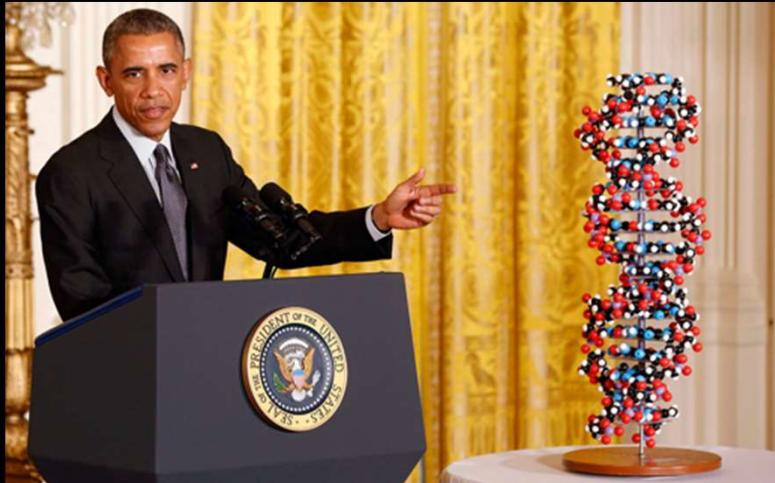
Spotlight News Profile Issues Did you know? In the media Impact



UCSF Medical Center at Mission Bay opens
Large-scale transport completed with support of city of San Francisco agencies. (CLICK IMAGE TO VIEW)



Big Data → Precision Medicine



"Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?"

- President Obama, January 30, 2015

My Group
Brian Le
Alice Taubes
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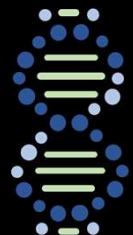
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Thanks!



Thanks!

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We are hiring!