

Computational Drug Discovery

Marina Sirota, PhD

Assistant Professor



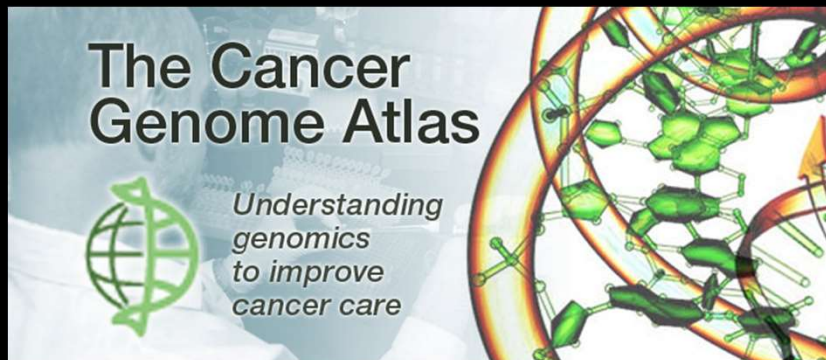
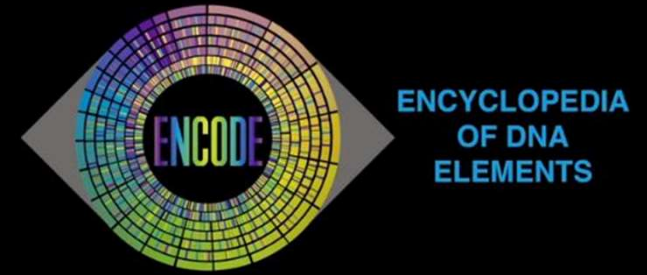
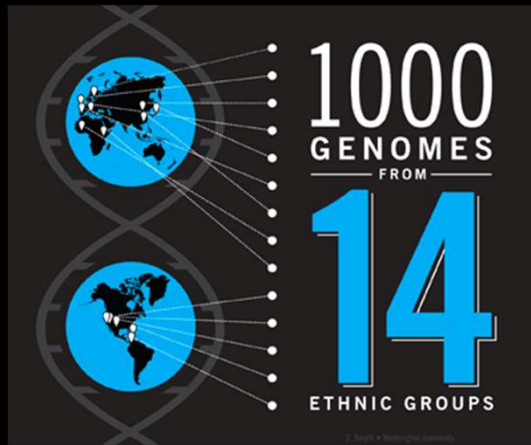
Sirota
Lab

UCSF

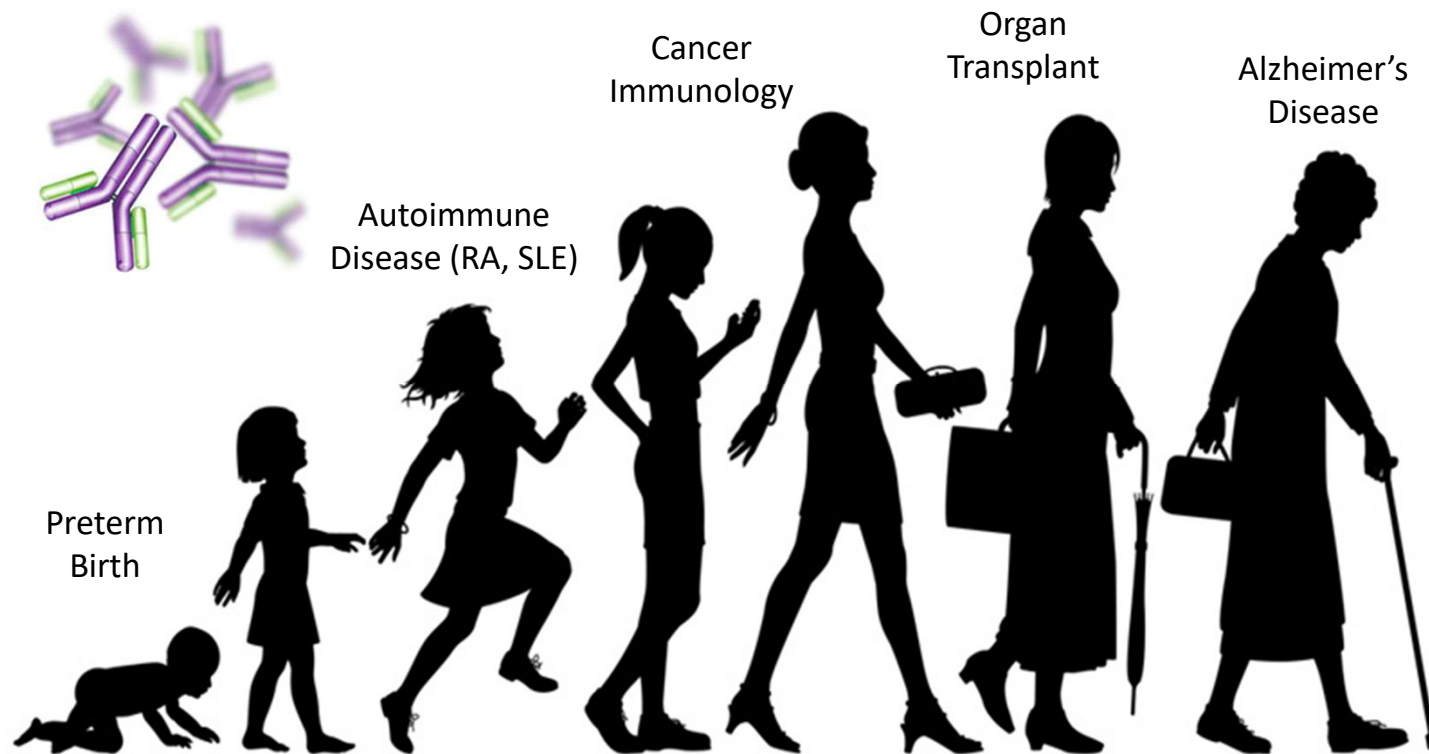
Bakar Computational Health
Sciences Institute



Why Now?



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

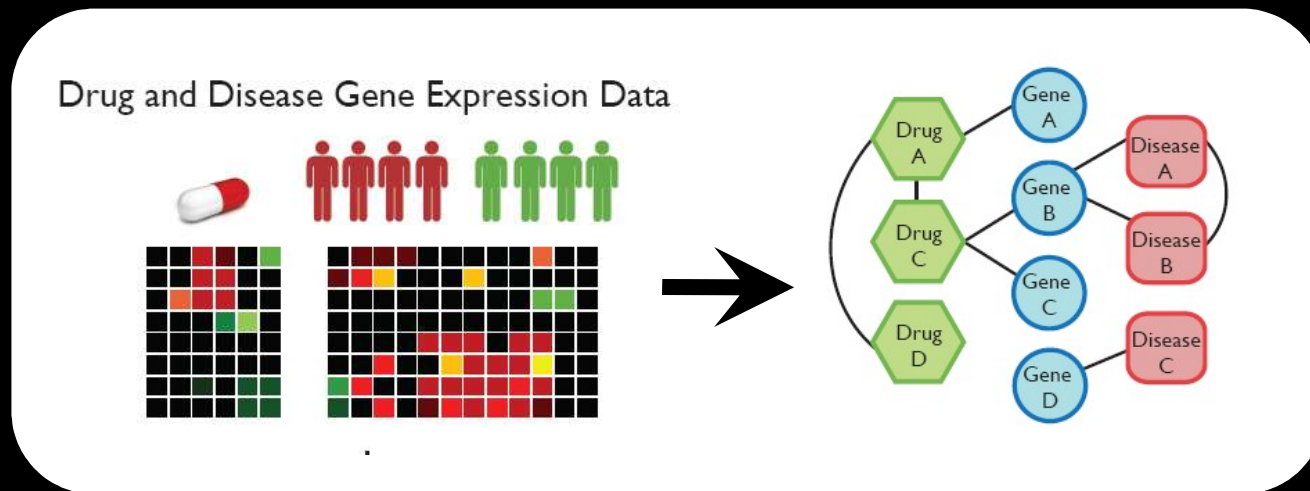


Computational Drug Repurposing

- 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

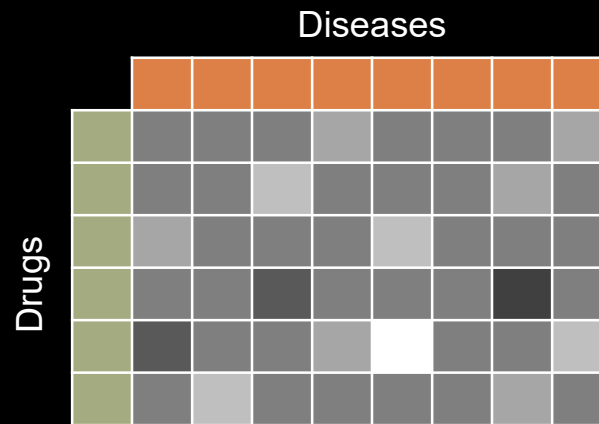
Can we use public data to systematically predict relationships between drugs and diseases?



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



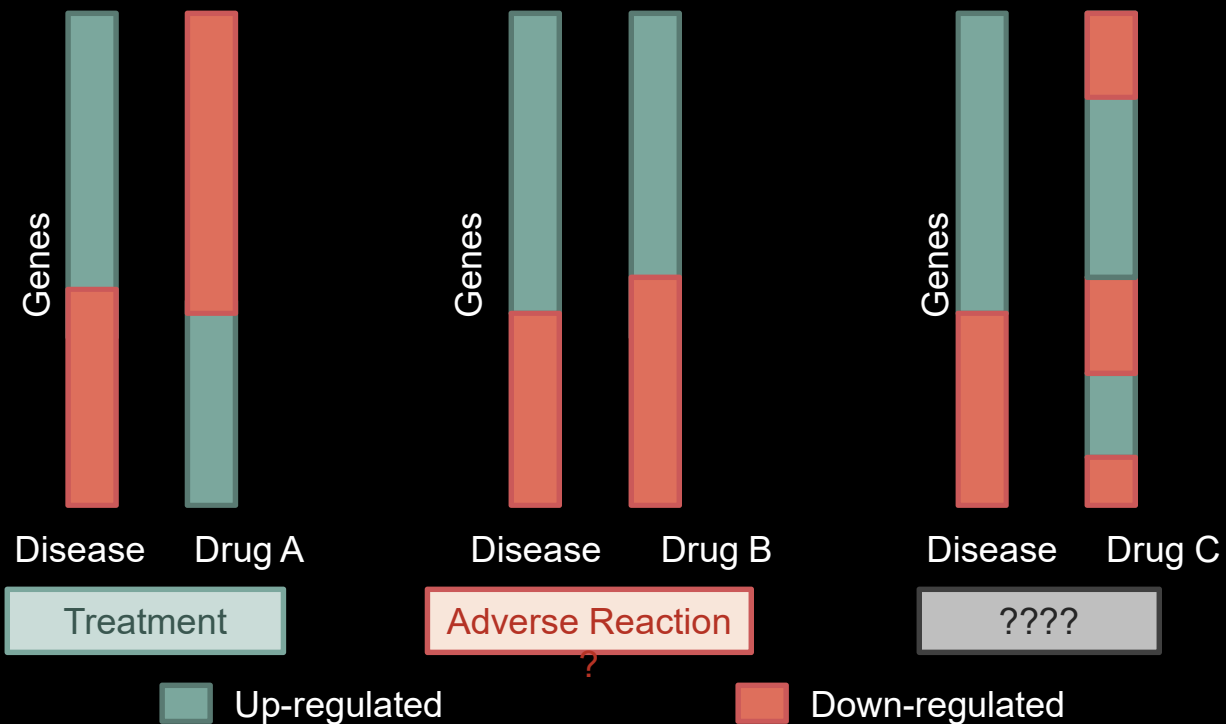
- Collection of expression data from cultured human cells
- Orig: 453 exprs of 164 drugs
- Now: 6,000 exprs, 1000+ drugs
- Covers broad range of effects
 - FDA approved drugs
 - Non drug bioactive small molecules

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



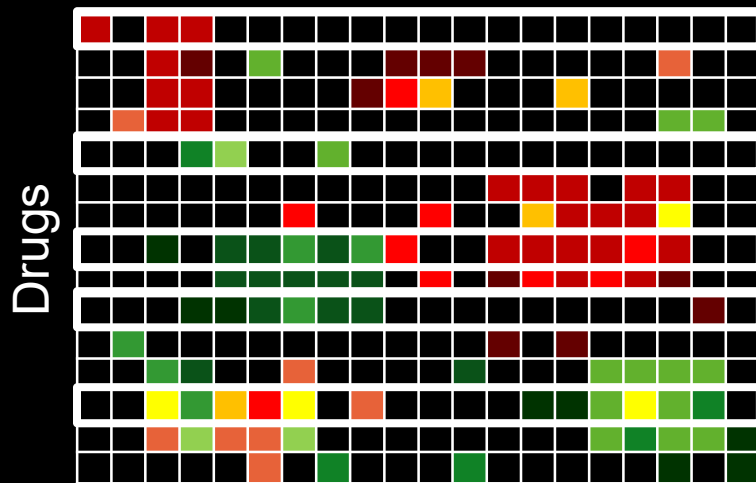
Lamb et al. The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease. Science. 2006.

Computational Pipeline

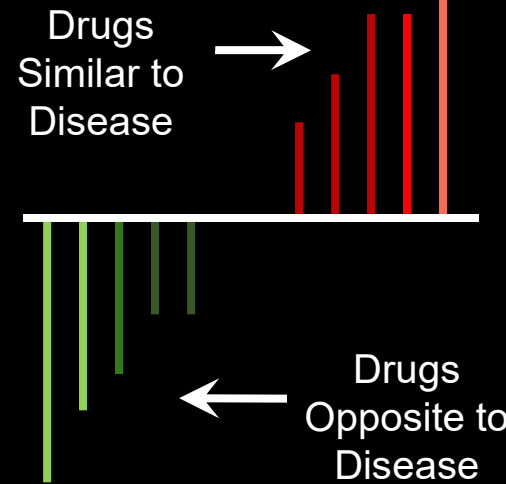
Disease Gene Expression Signature



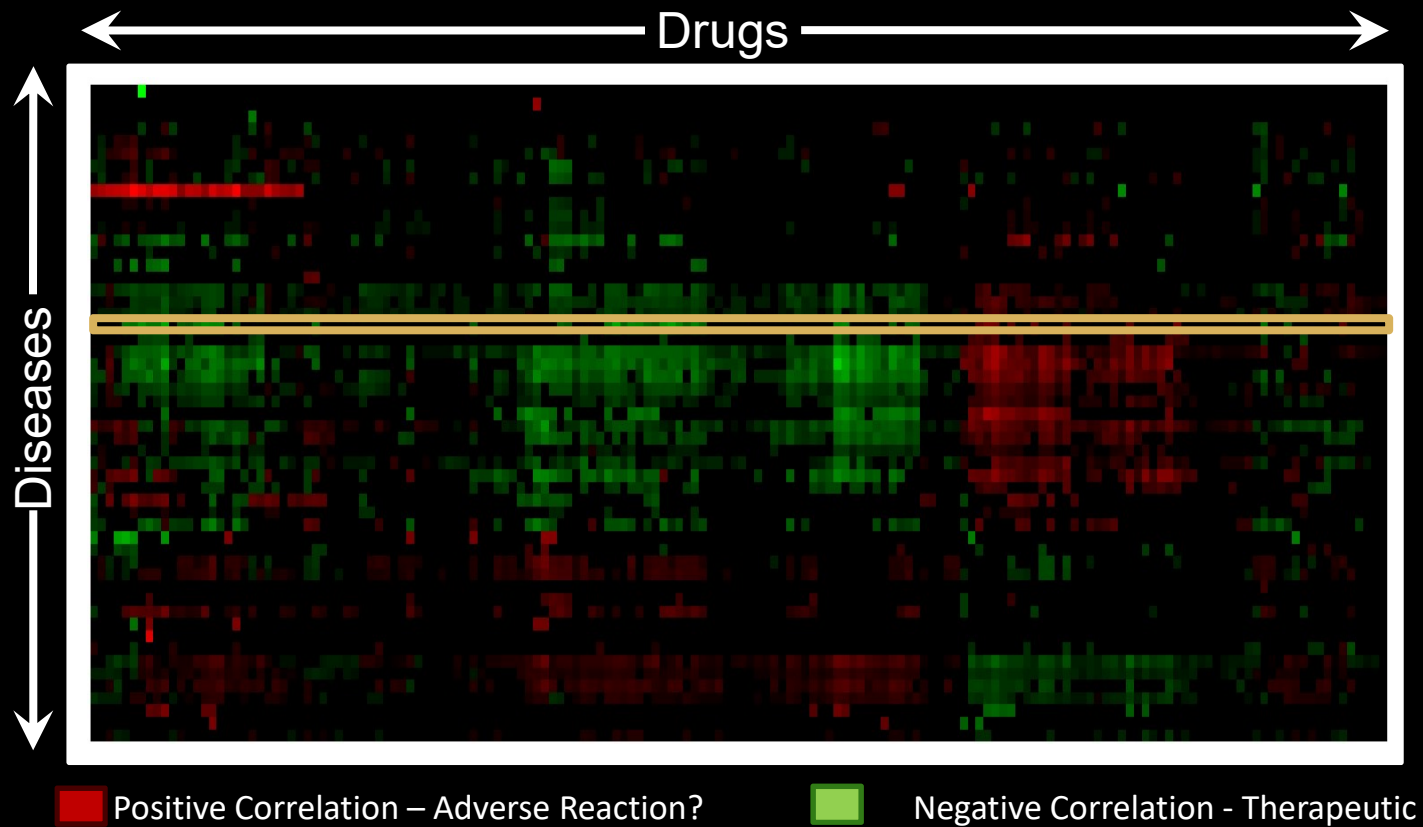
Genes



Disease-Drug Scores

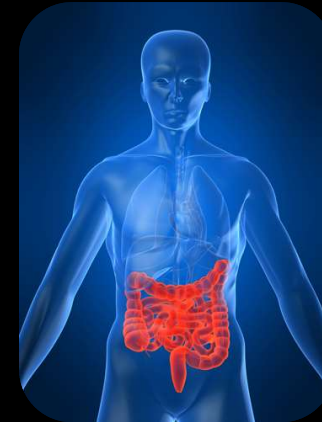


Drug-Disease Relationships

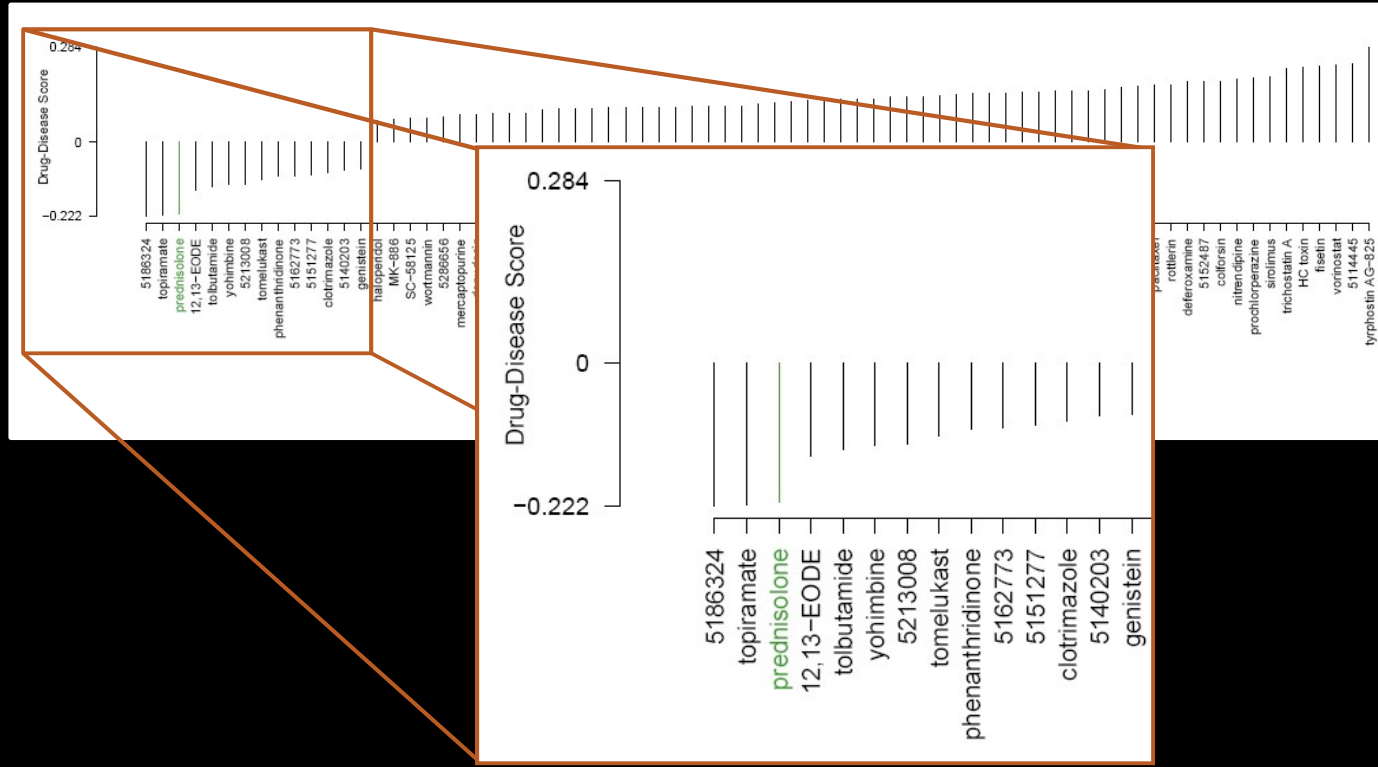


Crohn's Disease

- 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

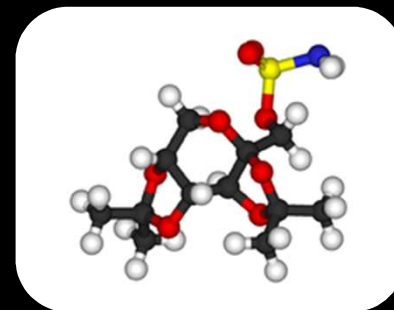


Therapeutic Predictions for Crohn's Disease

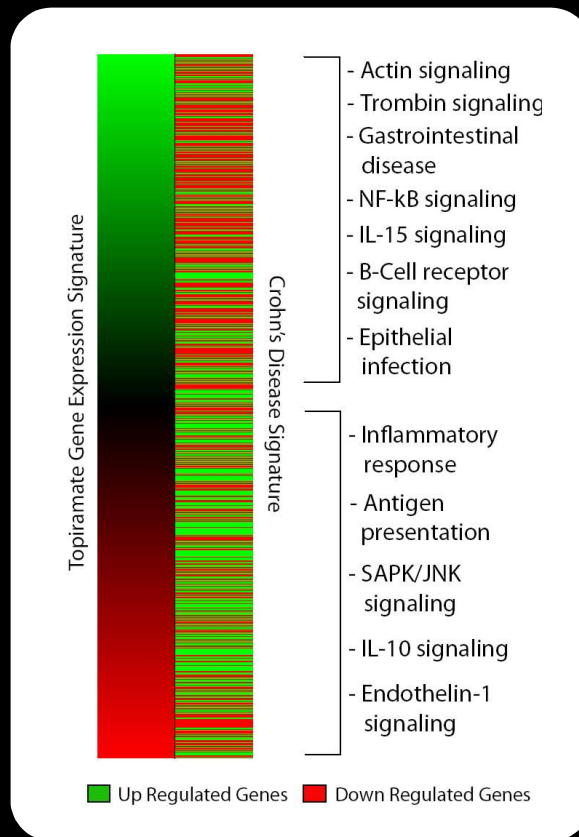


Topiramate – An Anti-Seizure Drug

- 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

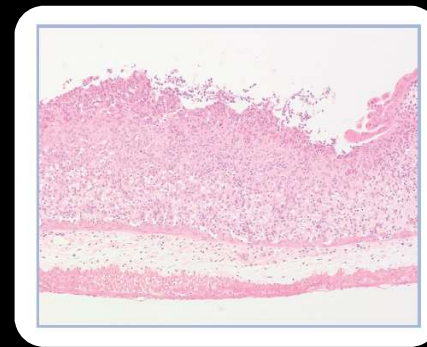
Genes that are
down-regulated by the drug are
up-regulated in the disease

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



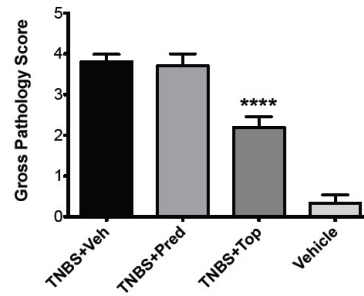
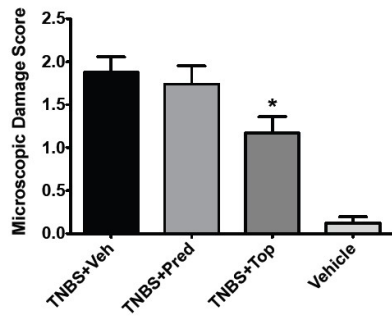
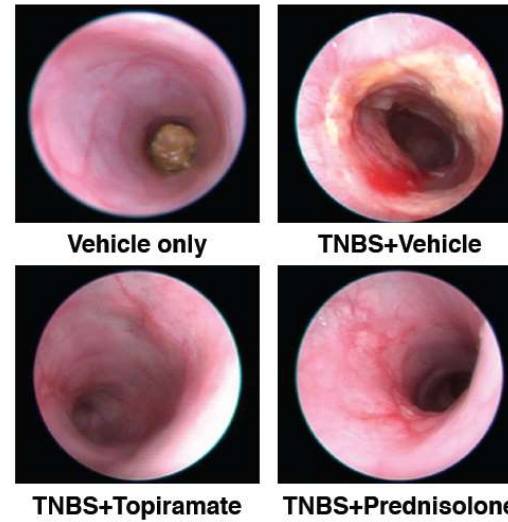
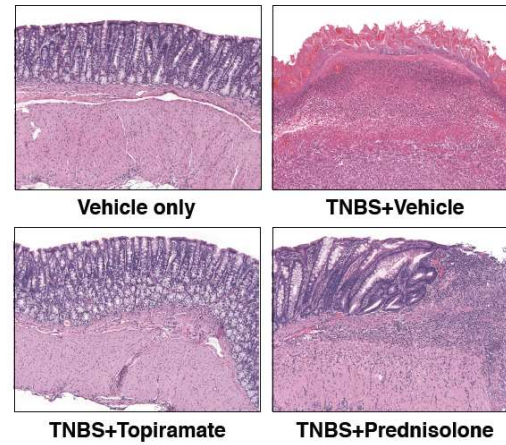
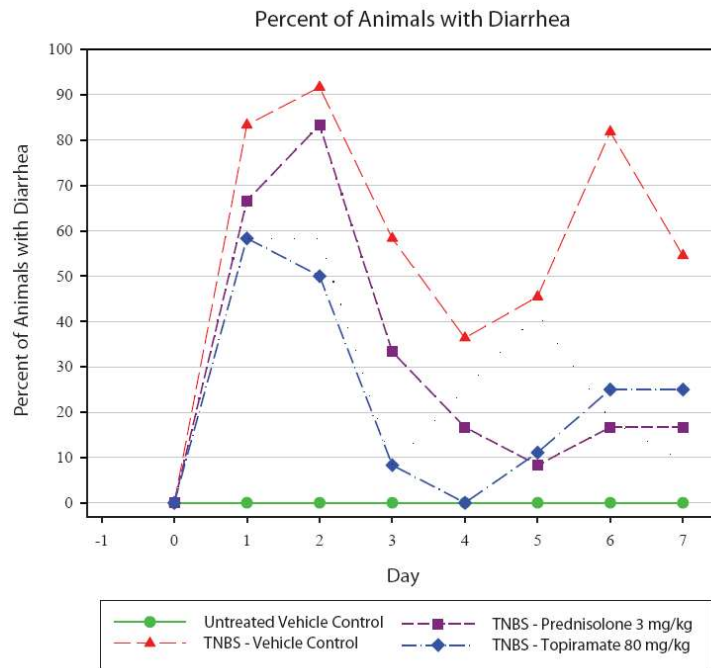
TNBS Induced

Two Follow-up Validation Studies

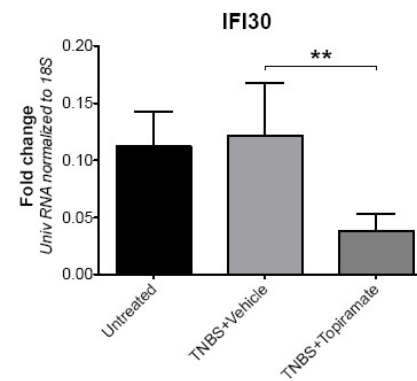
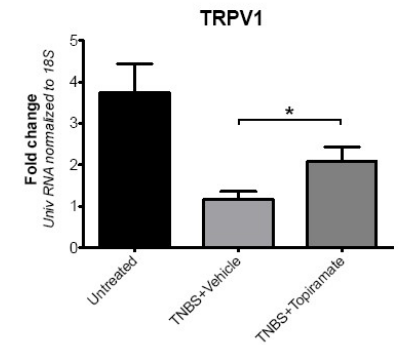
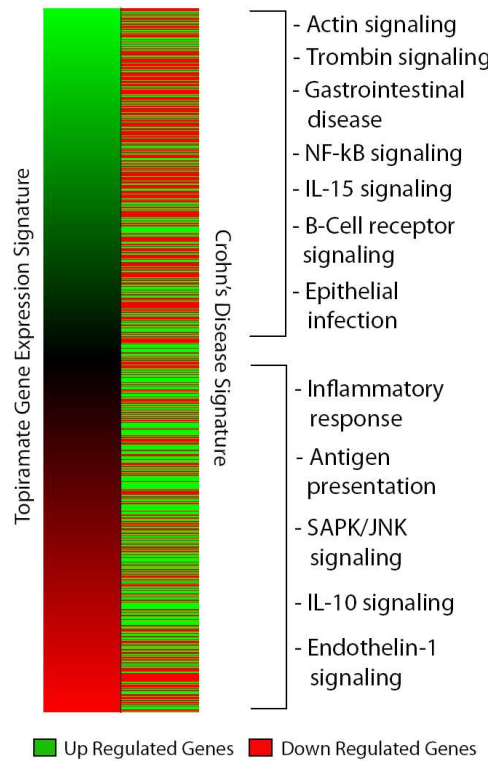
- 48 rats each – 4 groups of 12 rats
 - Healthy Controls
 - TNBS + Vehicle
 - TNBS + Prednisolone
 - TNBS + Topiramate
- 7 days
- Clinical Signs, Pathology Score, Histology
- Endoscopy Images



mbiosciences

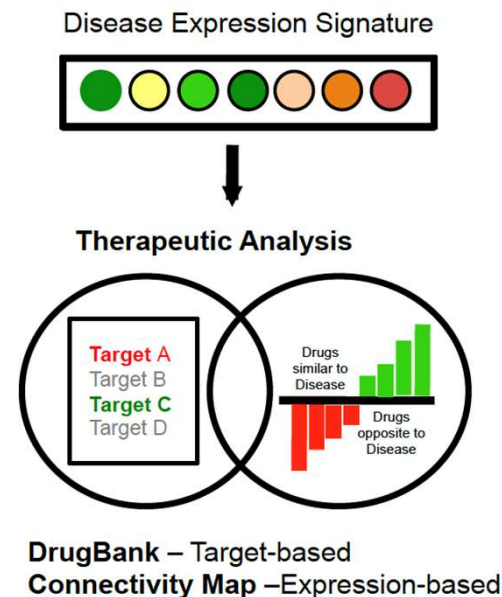


Drug-Disease Signature

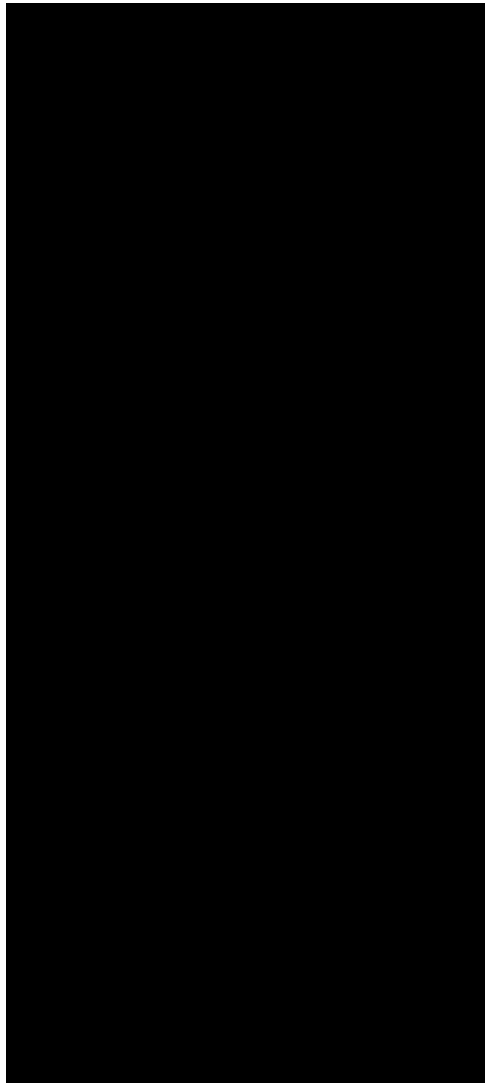


Application to Dermatomyositis

- 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.



288 Genes Downregulated

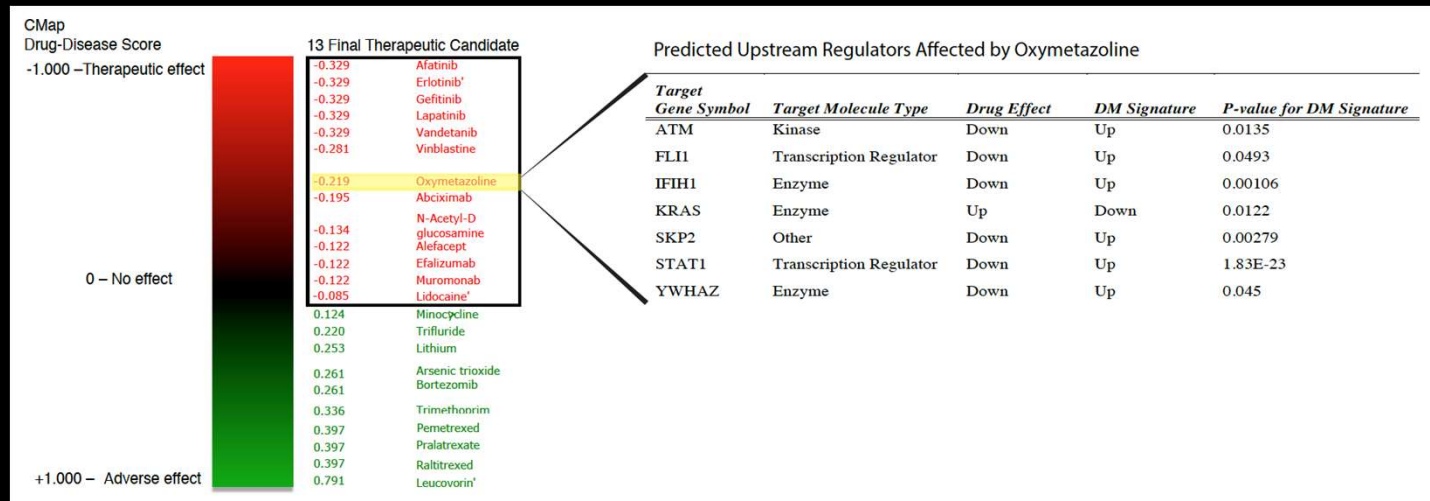
597 Genes Upregulated

Dermatomyositis Healthy Control

Healthy Control
Dermatomyositis
-8.0 +8.0
average fold change
relative to mean of all samples

- Connective Tissue Dev
 - JUN
 - NR4A1
 - NFKB1A
 - LRP6
 - BCL6
 - ...
- Antigen Presentation
 - TAP2
 - TARBP
 - HLA-E
- Signaling
 - CASP8
 - TLR1
 - TGFBR2
 - FCER1G
 - BMP4
- Epithelial Adherens Junction Remodeling
 - ARPC2
 - ARPC1A
 - DNM1L
- Protein Ubiquitination
 - B2M
 - USP28
 - UBE2N
 - UBE2J1
 - UBA13
 - UBE4B
- IFN Signaling
 - IFB5
 - IFIT3
 - STAT1
 - IFITM1
 - IRF9
 - IFIT1
- Cell Cycle Regulation
 - CCND2
 - CCNE2
 - CDK1
- Toll-like Receptor
 - CXCL11
 - CXCL10
 - CXCL9
 - STAT1
 - TLR1
 - TLR3
 - TLR9

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

Letter to the Editor

Computational Identification of Topiramate as a Potent Dermatological Agent Using Public Gene Expression Data

Joel T. Dudley,^{1,2,3*} Mari Aleja,^{1,3} Silke Roedder,^{1,3} Ann Pankaj Jay Pasricha,⁴ Hyunje Grace Cho B.A., M.D., Ph.D.^{2,4} ✉

Identification of Alpha-Adrenergic Agonists as Potent Dermatological Agents Using Public Gene Expression Data

JCI INSIGHT

Hyunje Grace Cho B.A., M.D., Ph.D.^{2,4} ✉

- ¹ School of Medicine
- ² Department of Dermatology
- ³ Institute for Computational and Data Sciences
- ⁴ University of California, San Diego

RESEARCH ARTICLE

Combined inhibition of atypical PKC and

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b



Am
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ARTICLE

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

DOI: 10.1038/ncomms16022

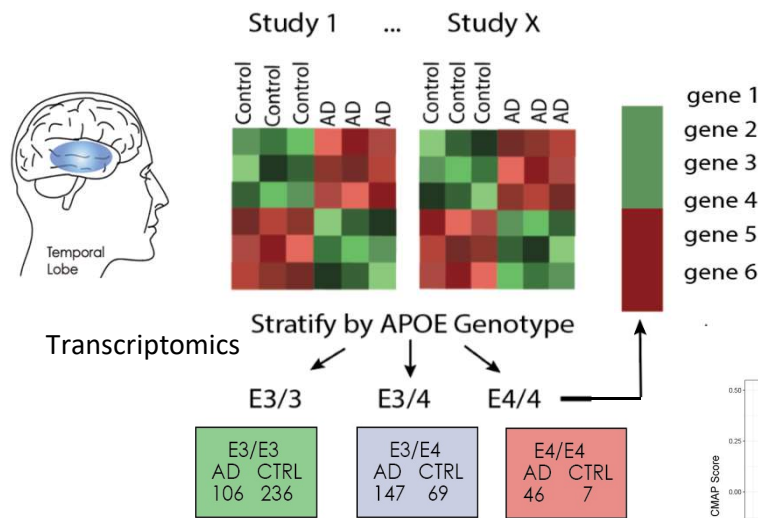
OPEN

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

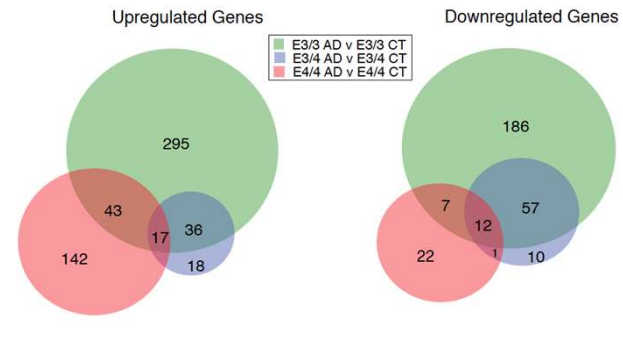
Bin Chen^{1*}, Li Ma^{2*}, Hyojung Paik^{1,3}, Marina Sirota¹, Wei Wei², Mei-Sze Chua², Samuel So² & Atul J. Butte¹

Precision Medicine Approach to Drug Repurposing: Alzheimer's Disease

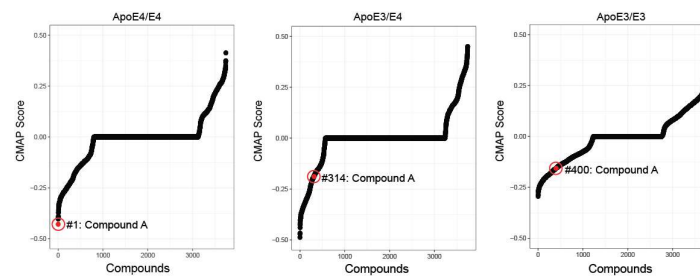
APOE-Specific Gene Expression Signatures of AD Leveraging Public Data



Unique APOE Specific Transcriptional Signatures



Computational Therapeutic Prediction



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

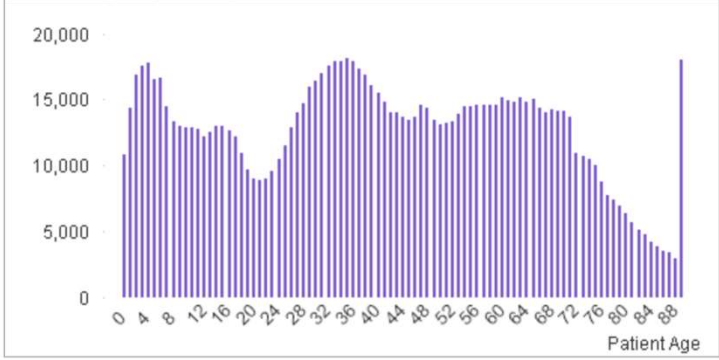


Patients 1,163,581 (100.0%)

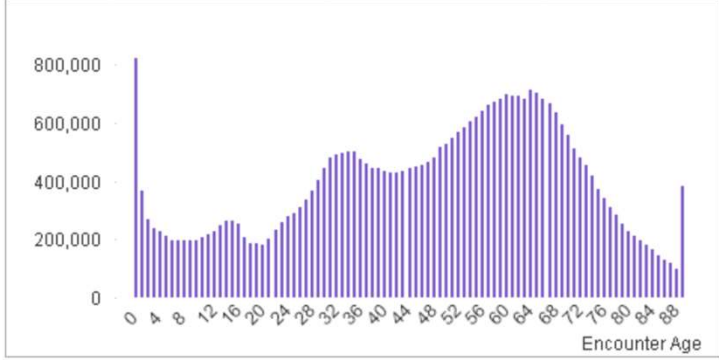
Deidentified patient data

Full View
 Top View

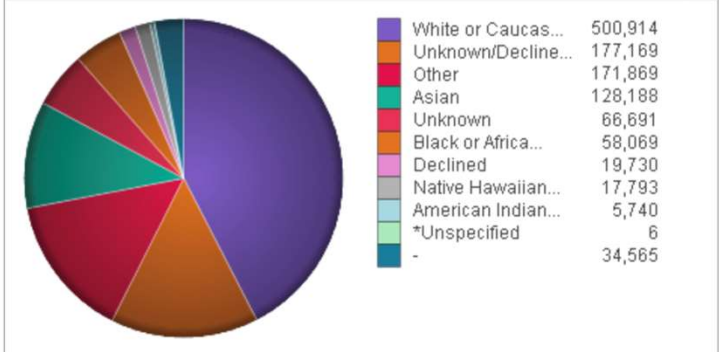
Patient Ages (current) [x] >>



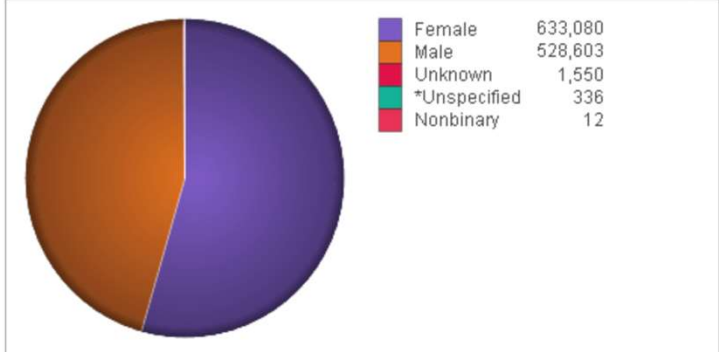
Patient Ages as of Encounter (count of encounters) [x] >>



Race [x] >>



Sex [x] >>





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

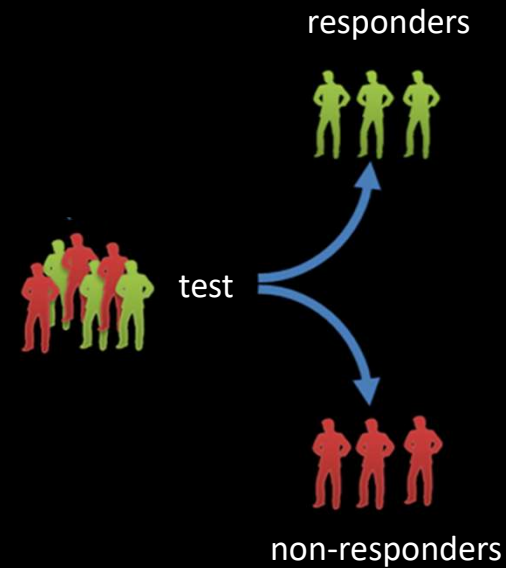
Spotlight News Profile Issues Did you know? In the media Impact



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



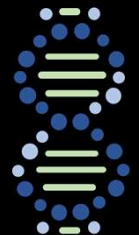
Big Data → Precision Medicine



"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

Acknowledgements



My Group

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Shan Andrews

Hongtai Huang

Silvia Pineda

Atul Butte

Joel Dudley

Alex Morgan

Mohan Shenoy

Grace Cho

Kavita Sarin

Matthew Lewis

David Fiorentino

Bin Chen

Hanna Paik

Julien Sage

Minnie Sarwal

Mei-Sze Chua

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Yadong Huang

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Thanks!



Thanks!

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We are hiring!