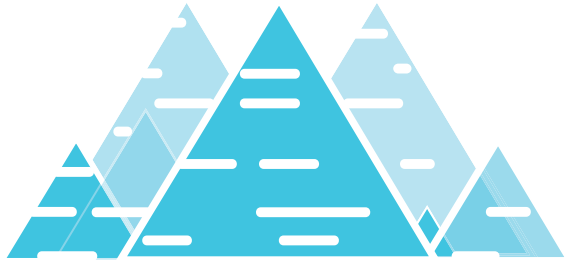

PERSONALIZED MEDICINE

SUMMIT

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June 7-9th 2015, UBC, Vancouver, BC

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#PMSummit2015

Connecting Precision Medicine to Precision Wellness towards a systems understanding of health and disease

Joel Dudley, PhD

Director of Biomedical Informatics &
Assistant Professor of Genetics and Genomic Sciences,
Icahn School of Medicine at Mount Sinai

Icahn School of Medicine at
Mount Sinai

@IcahnInstitute

Still bitter after all these years?

Alain Vigneault

Mount Sinai Health System

7

Member hospital campuses

>3,500

Hospital beds

>6,000

Physicians

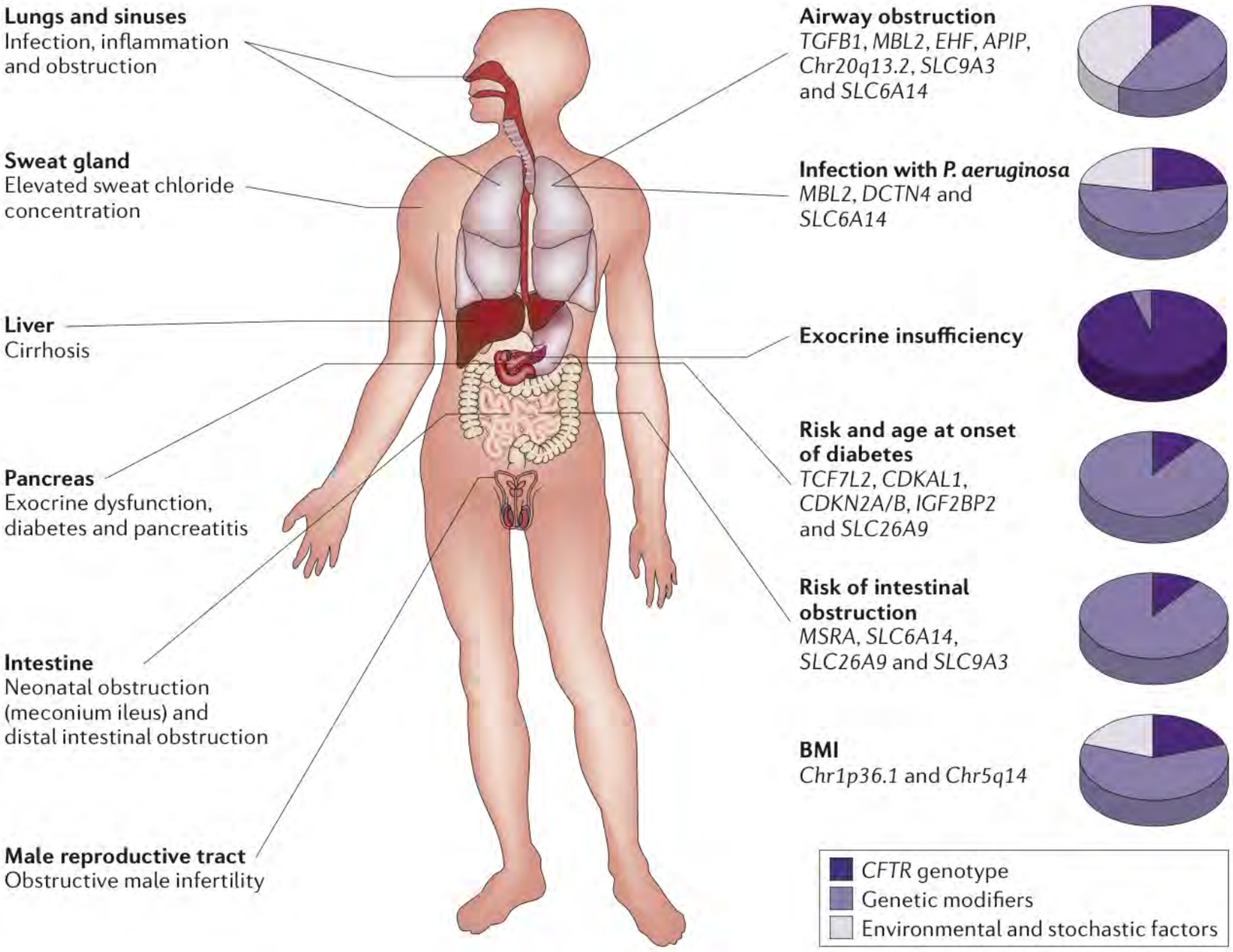
>3,100,000

Patient visits

There are rarely smoking guns in human health

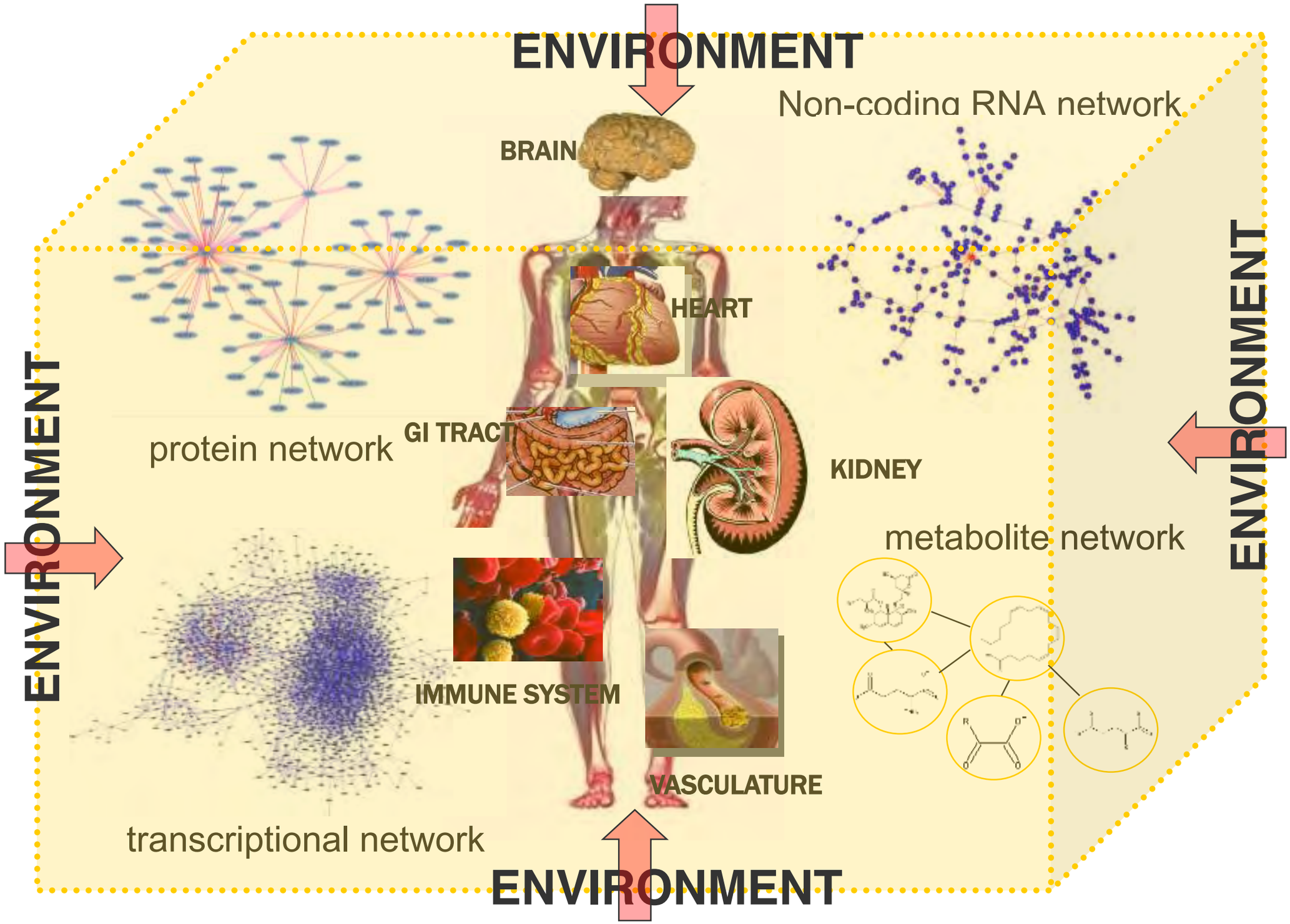
There are rarely smoking guns in human health

No such thing as a "simple" disease



Cutting GR. Nature Reviews Genetics. (2014) doi:10.1038/nrg3849

We must embrace complexity to fully understand patient physiology and disease



We must embrace complexity to fully understand patient physiology and disease

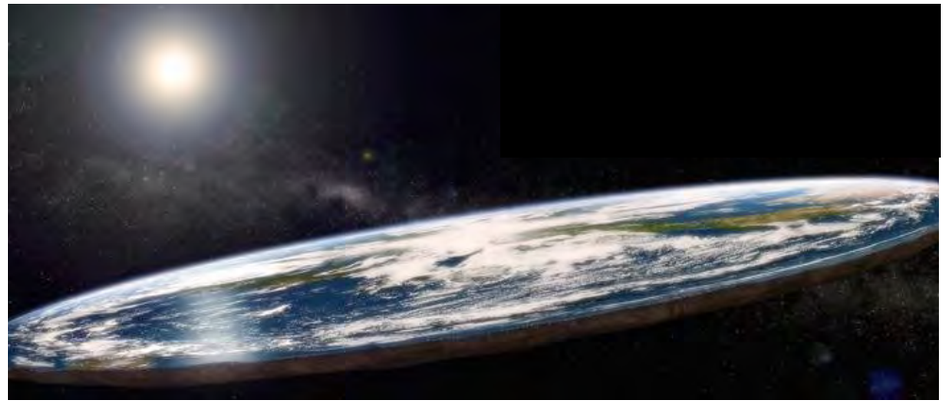
lex adaptive system has three characteristics. The that the system consists of a number of neous agents, and each of those agents makes s about how to behave. The most important n here is that those decisions will evolve over e second characteristic is that the agents interact with one another. That interaction leads to the third—something that scientists call emergence: In a very real way, the whole becomes greater than the sum of the parts. The key issue is that you can't really understand the whole system by simply looking at its individual parts".

- Michael J. Mauboussin (investment banker)

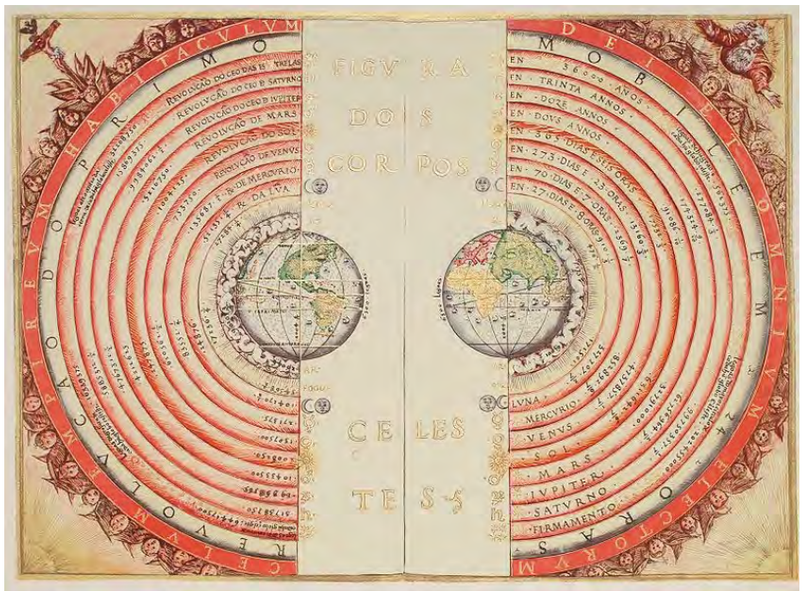
Although our ability to embrace complexity will bump up against our want to tell stories

Zeus, the sky god; when he is angry he throws lightening bolts out of the sky

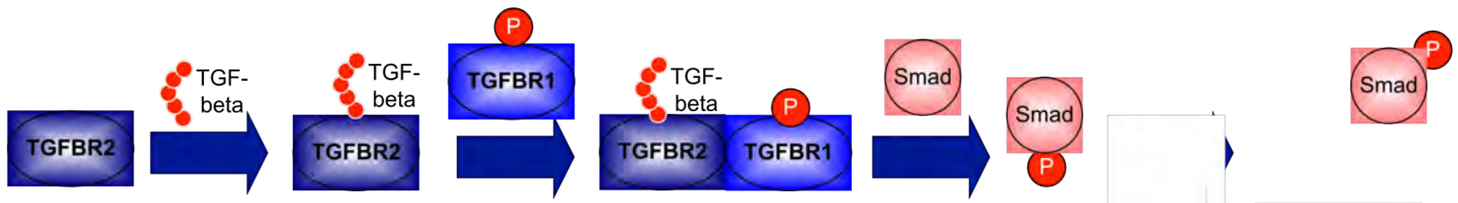
The earth is flat



Ptolemaic astronomy: the earth is the center of the universe



Biological processes are driven by simple linearly ordered pathways (e.g. TGF-beta signaling)



Who wants to hear actors talk?

– H.M. Warner
Warner Brothers, 1927

There is no reason anyone would want a computer in their home

– Ken Olsen
Founder and president of Digital Equipment Corp., 1977

Anyone who thinks the ANC is going to run South Africa is living in cloud-cuckoo-land

– Margaret Thatcher
British Prime Minister, 1987

I think there is a world market for maybe five computers

– Thomas Watson
Chairman of IBM, 1943

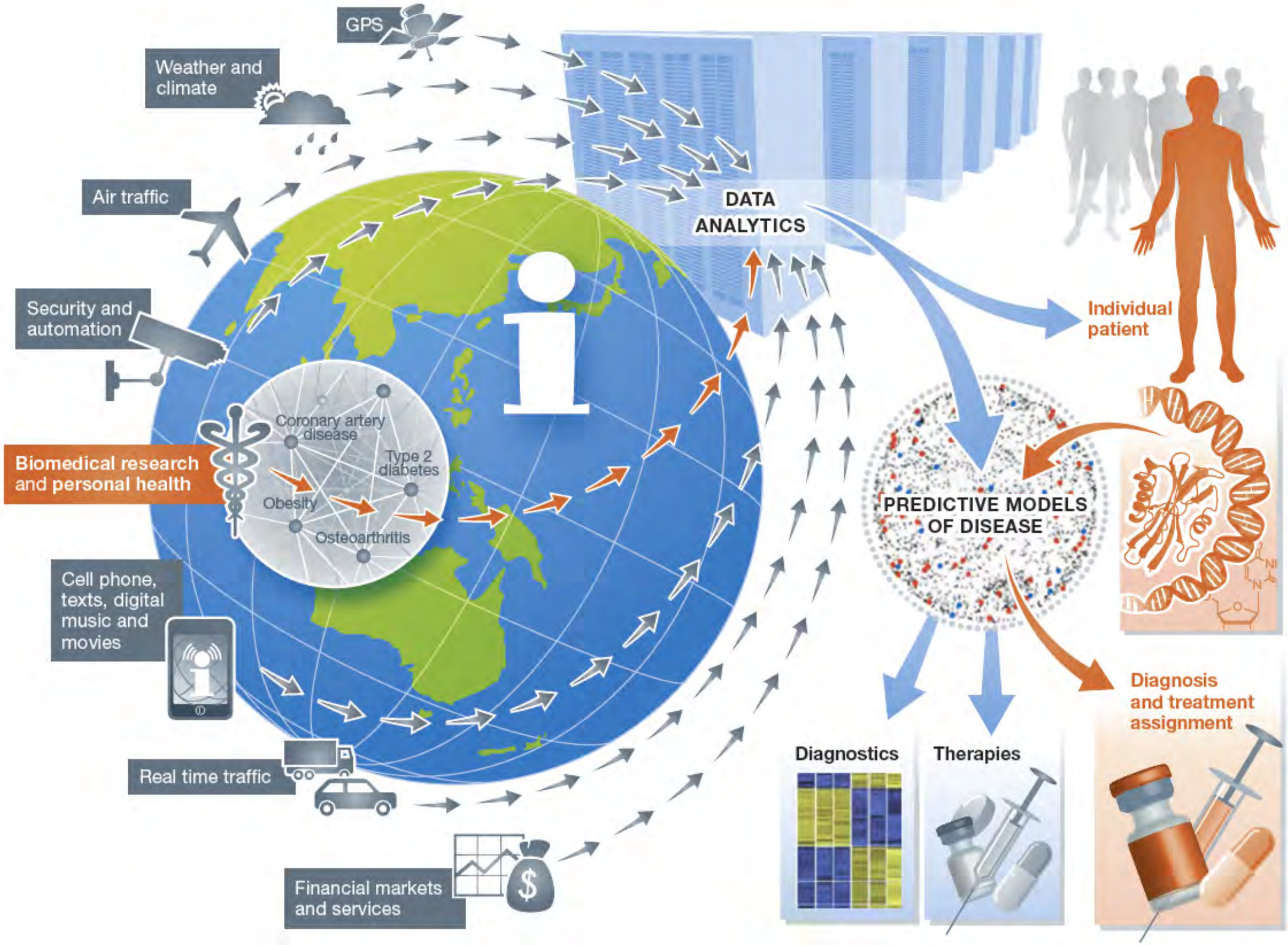
There will never be a bigger plane built

– A Boeing engineer after first flight of the 247, a 10-seater

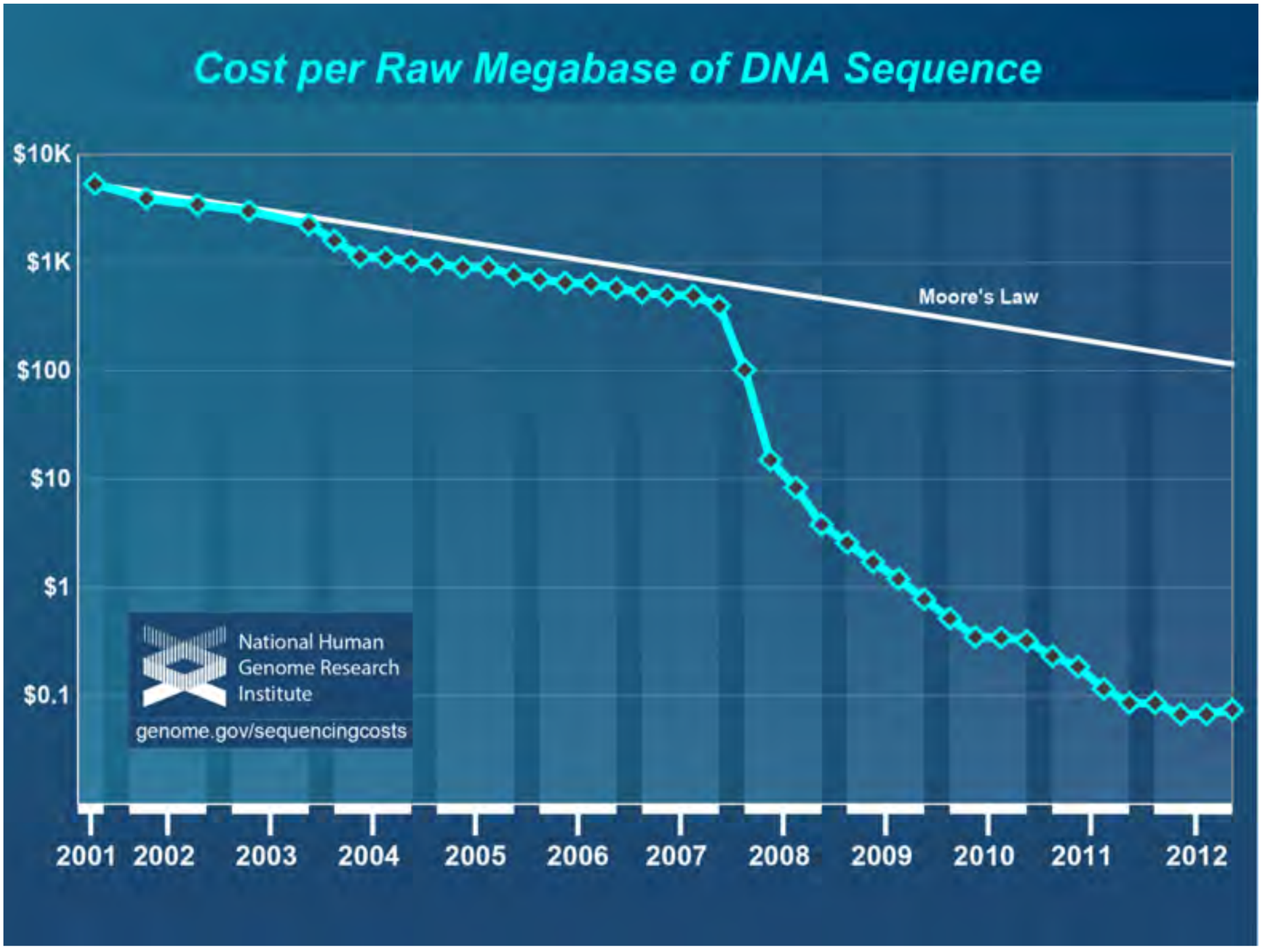
Biological processes are organized into simple pathways

– Life and Biomedical Sciences

Icahn Institute for Genomics and Multiscale Biology

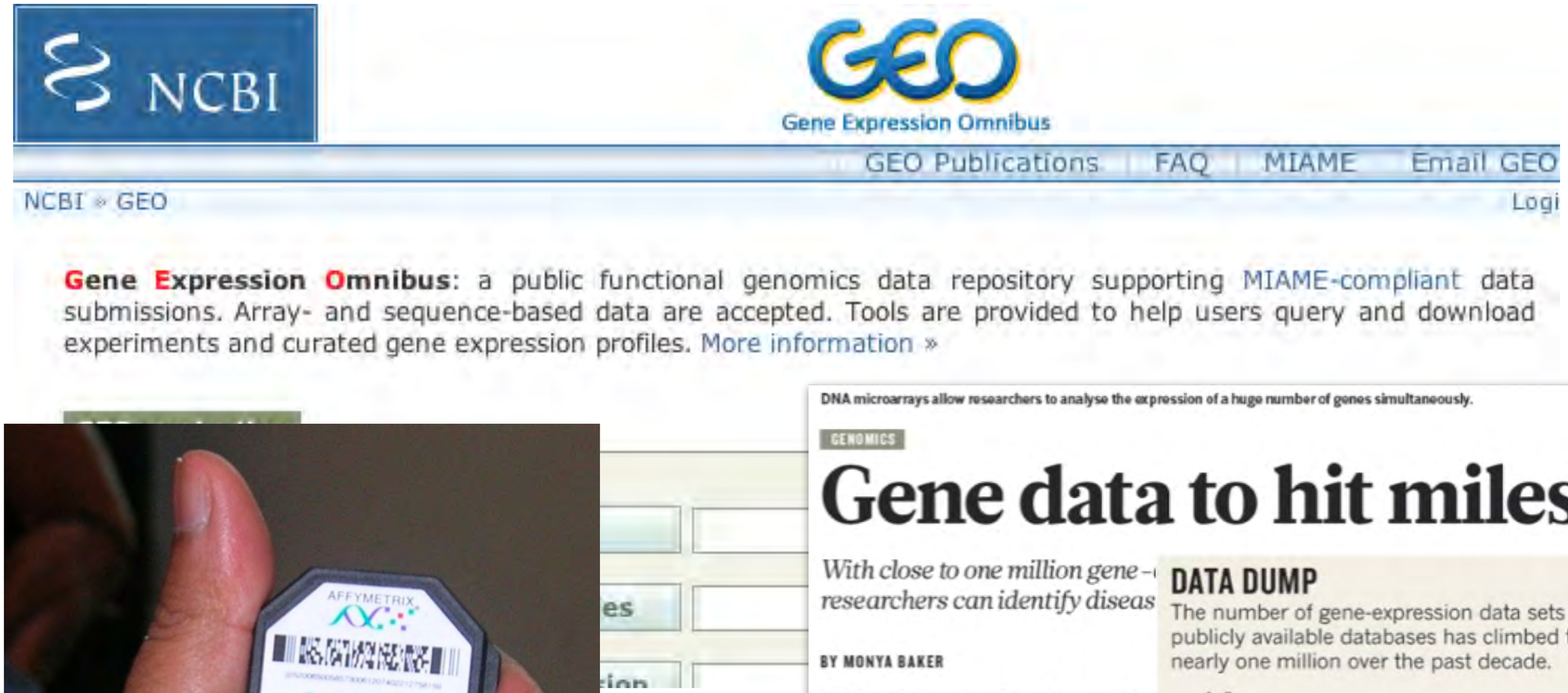


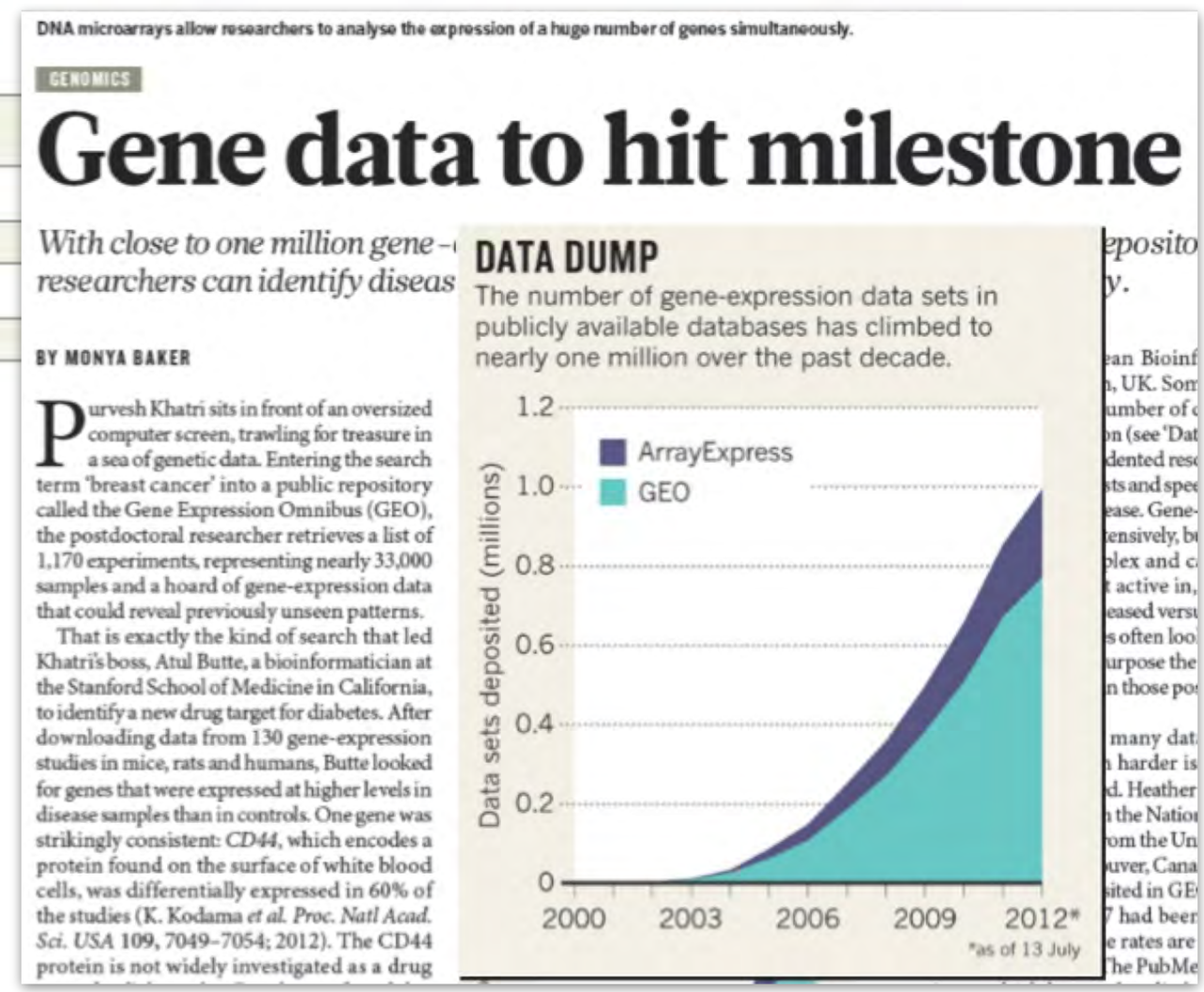
Being masters of really big data is now critical for biomedical research (TB→PB→EB→ZB)



Organisms → **Tissues** → **Single cells** → **Single cell, real-time, continuous?**

We can measure more than we know





DNA microarrays allow researchers to analyse the expression of a huge number of genes simultaneously.

GENOMICS

Gene data to hit milestone

With close to one million gene- ... *eposito*
researchers can identify diseas ... *y.*

BY MONYA BAKER

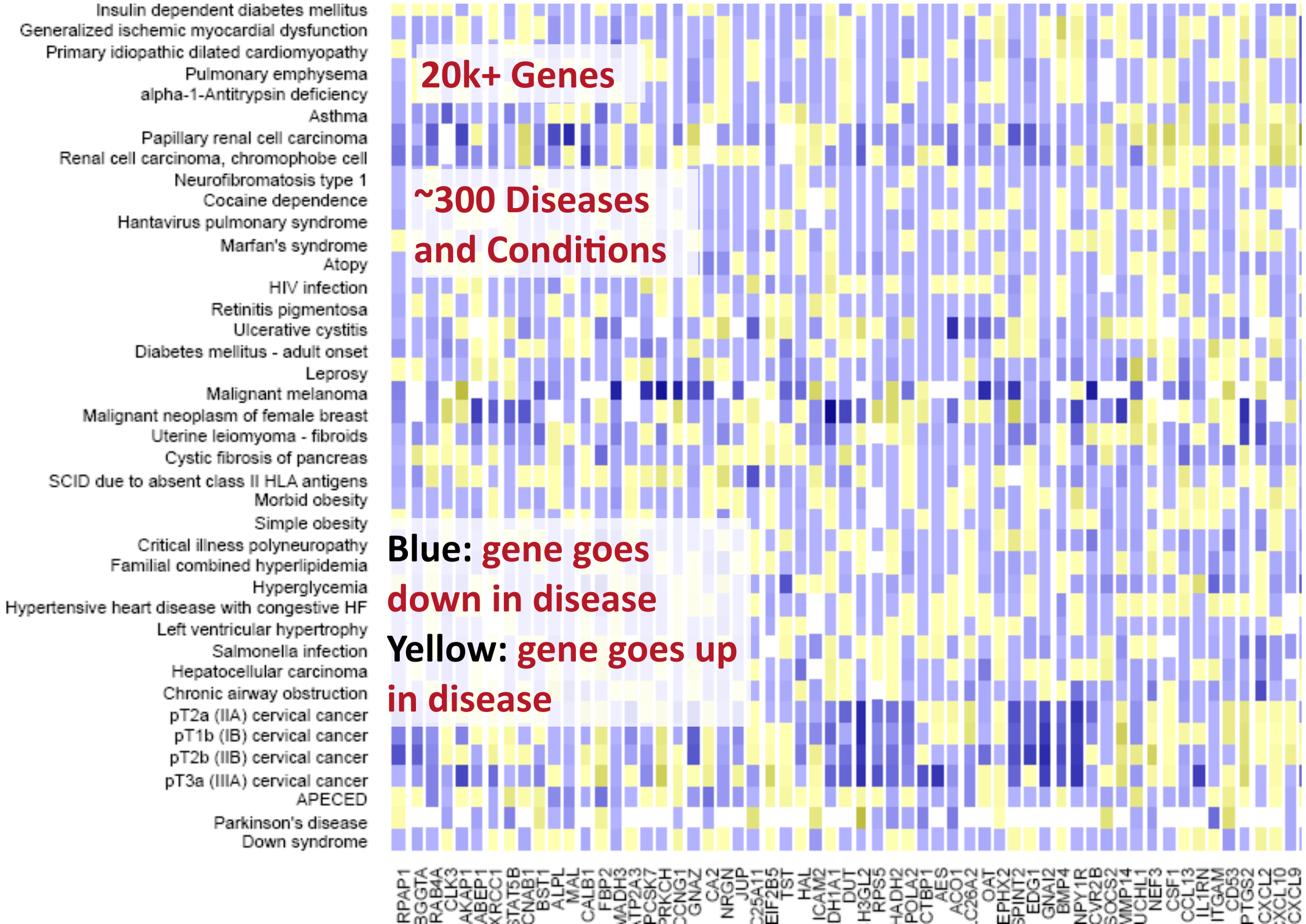
Purvesh Khatri sits in front of an oversized computer screen, trawling for treasure in a sea of genetic data. Entering the search term 'breast cancer' into a public repository called the Gene Expression Omnibus (GEO), the postdoctoral researcher retrieves a list of 1,170 experiments, representing nearly 33,000 samples and a hoard of gene-expression data that could reveal previously unseen patterns.

That is exactly the kind of search that led Khatri's boss, Atul Butte, a bioinformatician at the Stanford School of Medicine in California, to identify a new drug target for diabetes. After downloading data from 130 gene-expression studies in mice, rats and humans, Butte looked for genes that were expressed at higher levels in disease samples than in controls. One gene was strikingly consistent: *CD44*, which encodes a protein found on the surface of white blood cells, was differentially expressed in 60% of the studies (K. Kodama *et al. Proc. Natl Acad. Sci. USA* 109, 7049–7054; 2012). The CD44 protein is not widely investigated as a drug

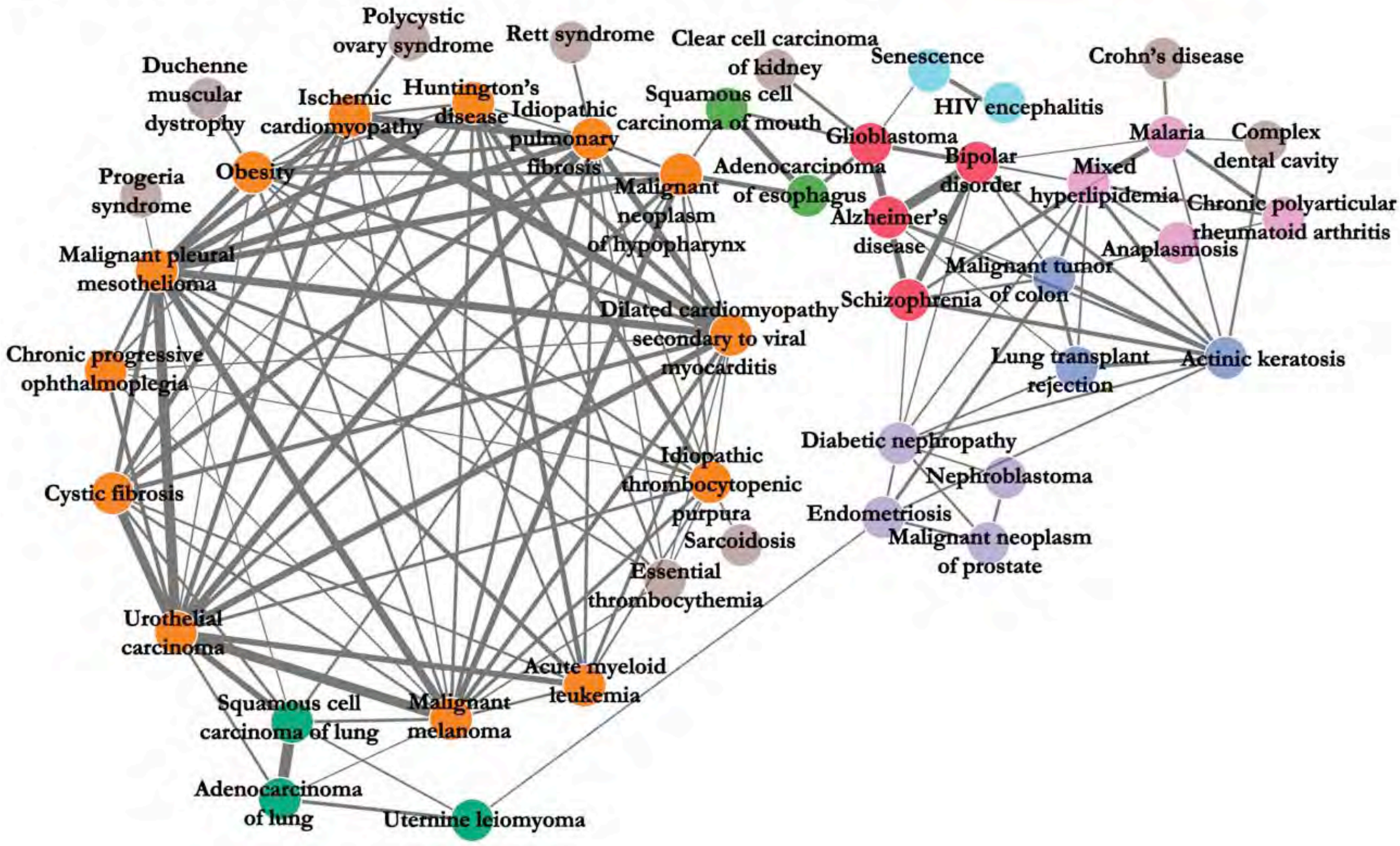
DATA DUMP

The number of gene-expression data sets in publicly available databases has climbed to nearly one million over the past decade.

Exploring the transcriptional landscape of human disease

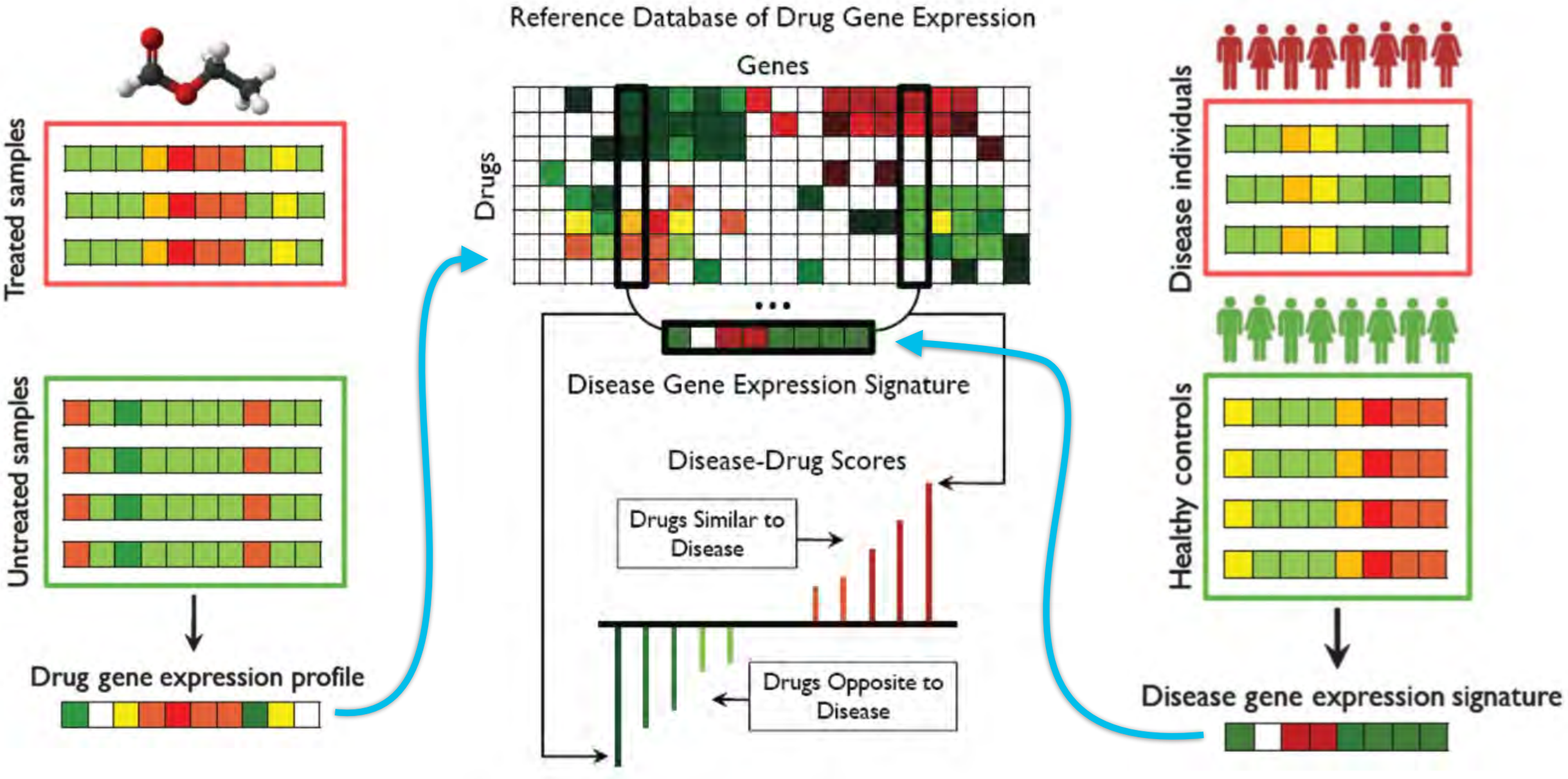


Redefining disease with data



Suthram S, Dudley J et al. Network-based elucidation of human disease similarities reveals common functional modules enriched for pluripotent drug targets. PLoS Computational Biology (2010)

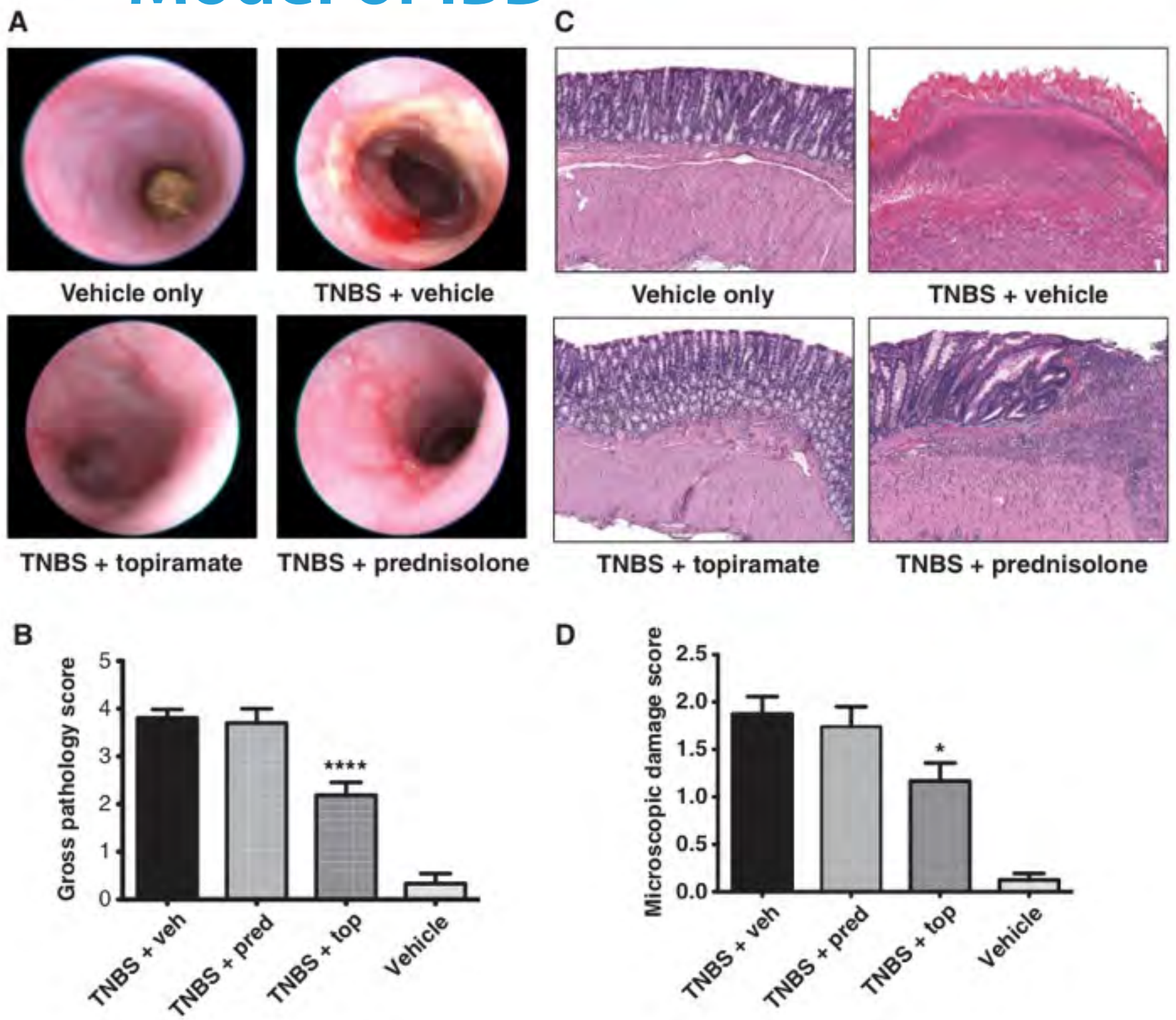
Data Driven Approach to Connect Drugs and Disease Using Molecular Profiles



Sirota, M., Dudley, J. T., et al. (2011). Discovery and Preclinical Validation of Drug Indications Using Compendia of Public Gene Expression Data. *Science Translational Medicine*, 3(96).

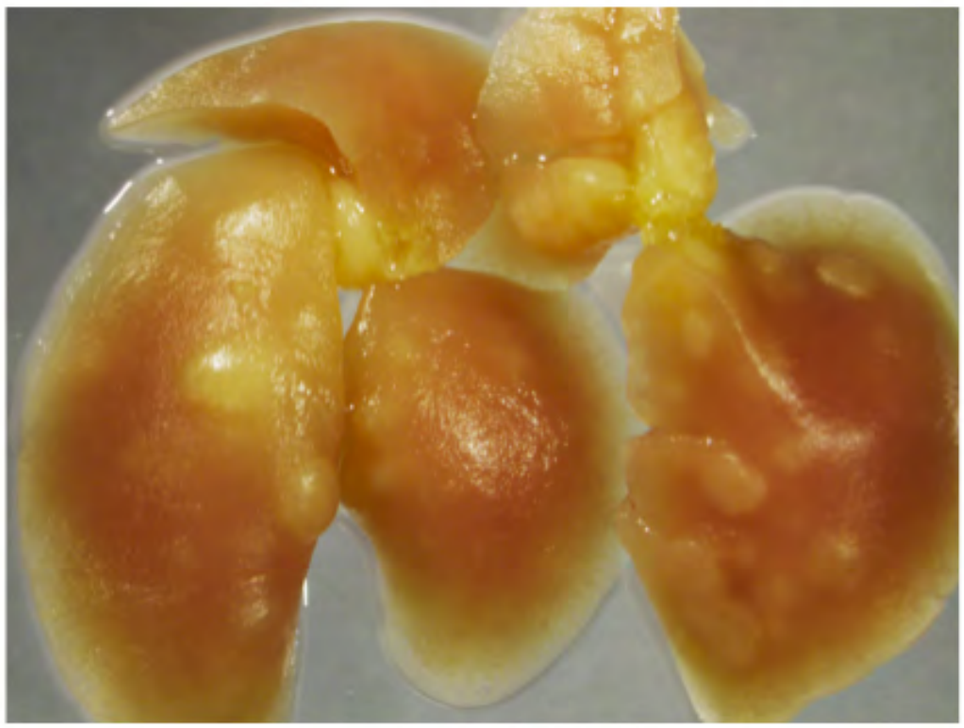
Topiramate Reduces IBD Severity in a TNBS Rodent Model of IBD

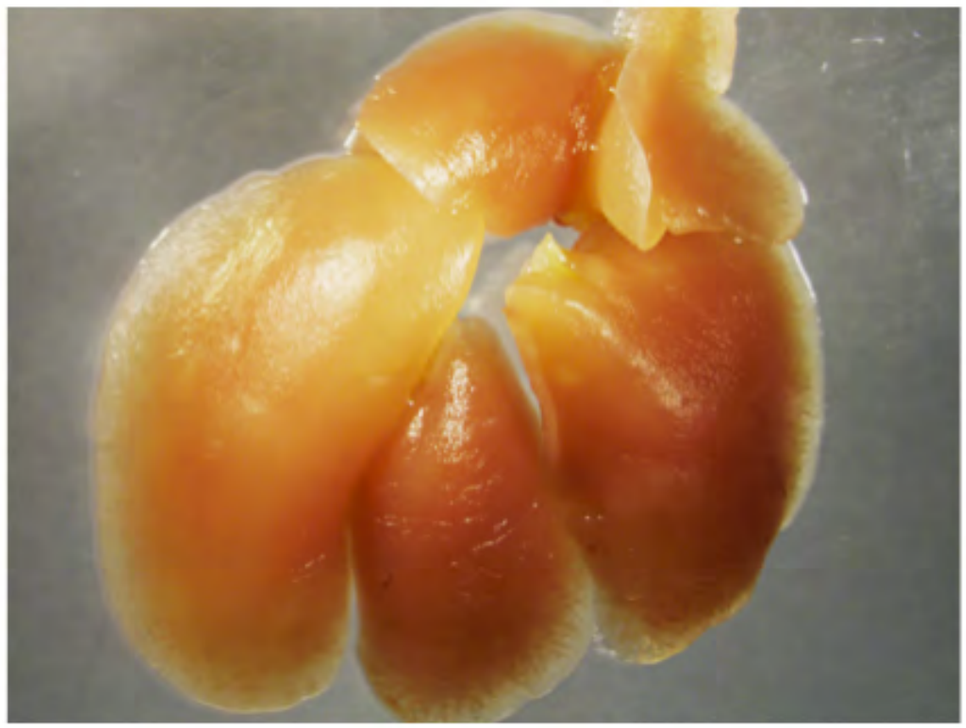
- TNBS chemically induced rat model of IBD
- Animals treated with 80mg/kg topiramate oral after sensitization
- Prednisolone positive control (approved for IBD in humans)



Dudley, J. T., Sirota, M., et al. (2011). Computational Repositioning of the Anticonvulsant Topiramate for Inflammatory Bowel Disease. Science Translational Medicine, 3(96).

Approved compound for non-cancer indication prevents formation of SCLC tumors in a genetic model of SCLC



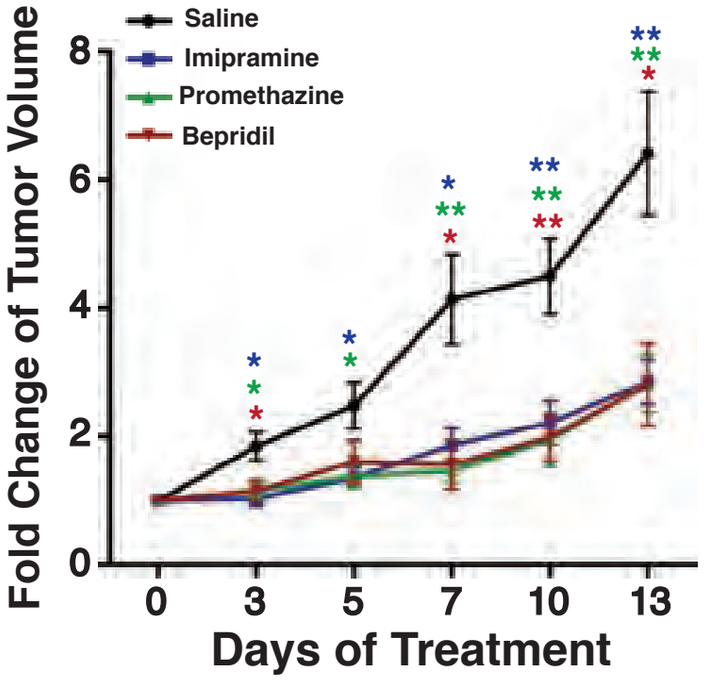


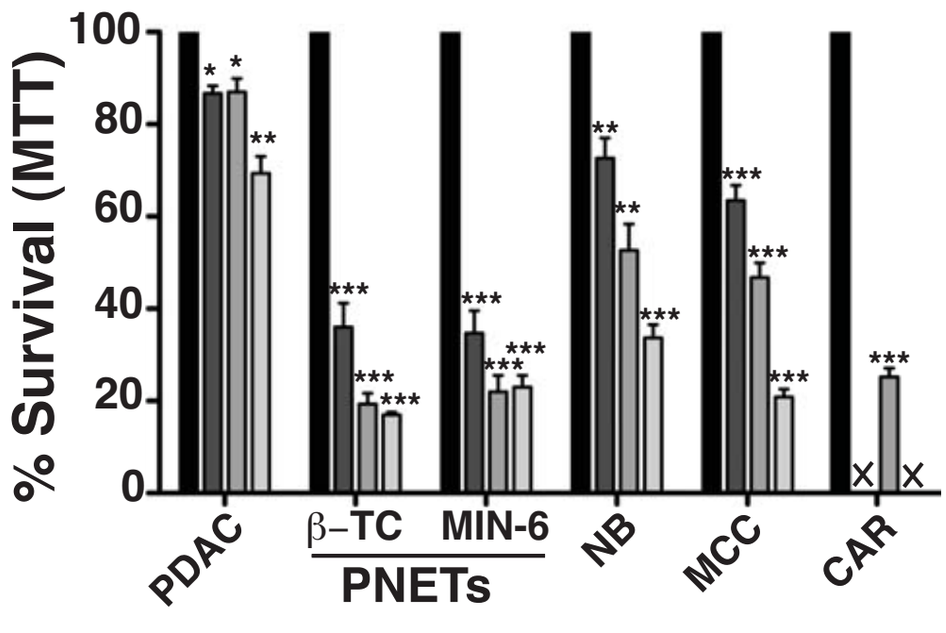
p53/Rb/p130 triple knockout model of SCLC

Control

Imipramine

b

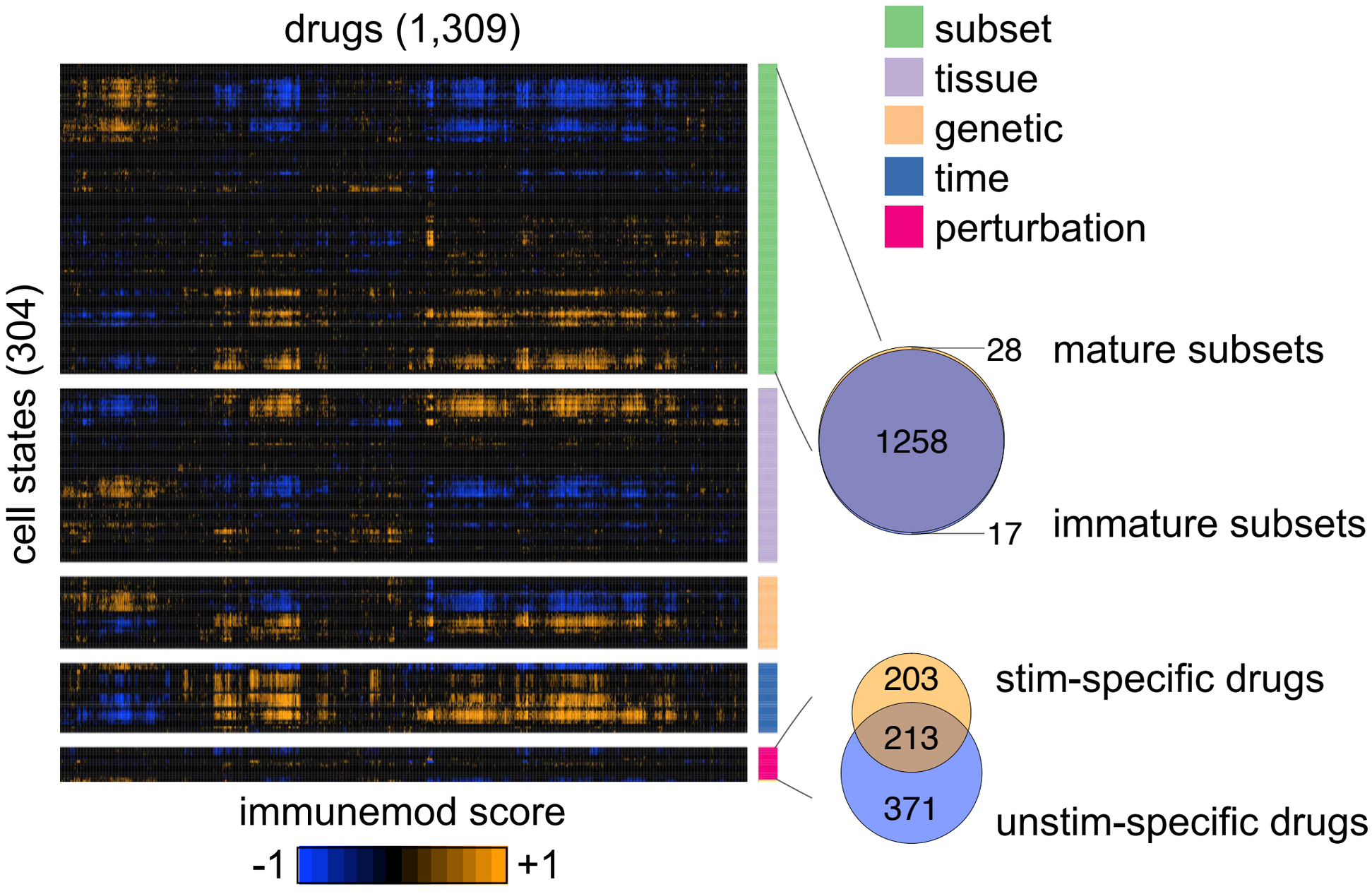




Mice dosed after tumor formation

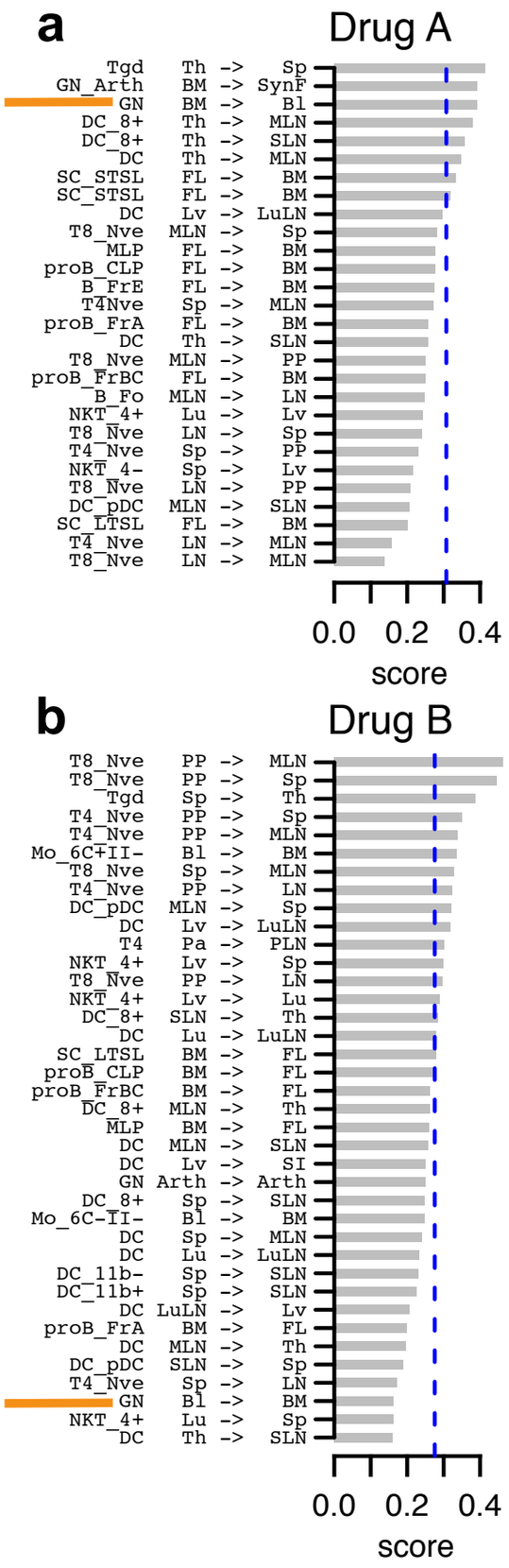
Control
Imipramine 30μM
Imipramine 50μM
Imipramine 75μM

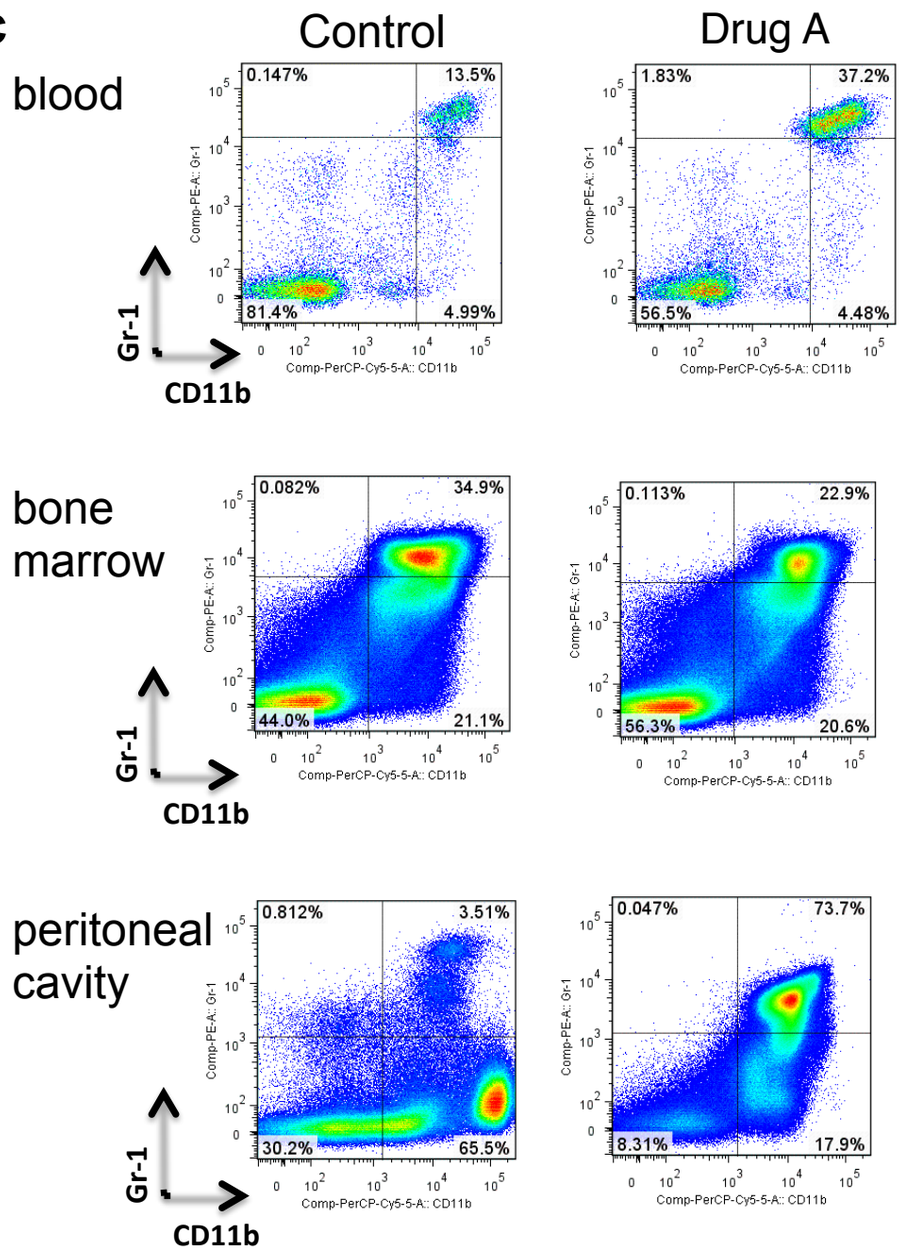
How do approved drugs modulate networks in immune cells?

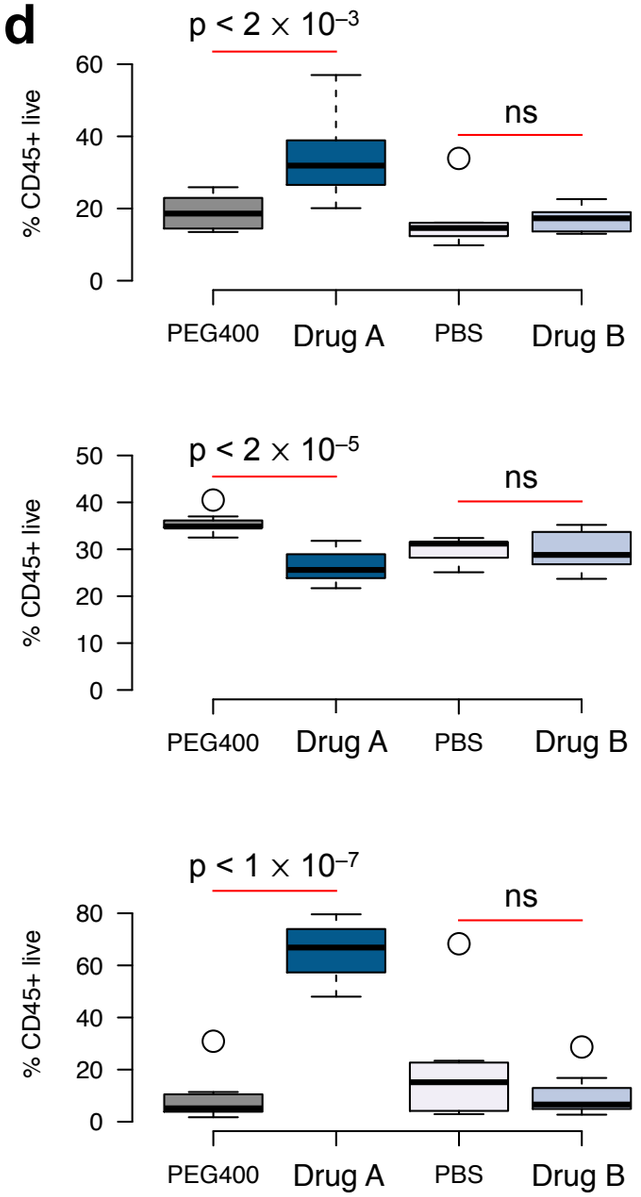


Kidd BA, Wroblewska A, Agudo J, Merad M, Brown BD, Dudley JT. Systematic integrative analysis of immune pharmacology. *In review.*

Antifungal activates neutrophil migration

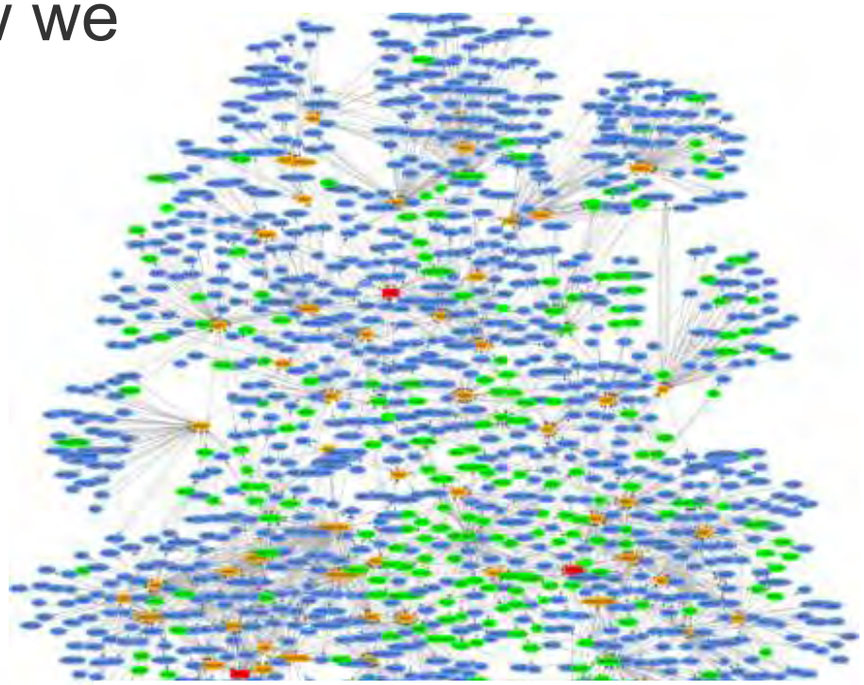






Kidd BA, Wroblewska A, Agudo J, Merad M, Brown BD, Dudley JT. Systematic integrative analysis of immune pharmacology. *In review.*

What we are about: Integrating big data across many domains to build predictive models that improve how we diagnose and treat disease

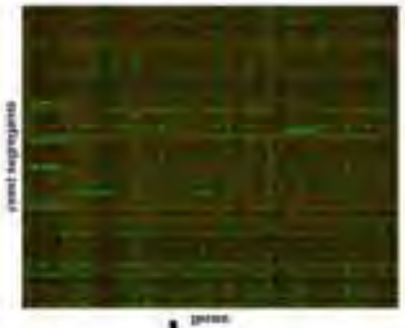


Predictive Network Model

Population

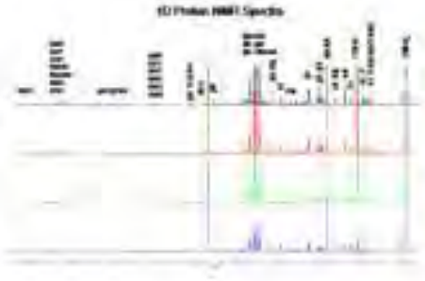
Sample acquisition

Gene expression

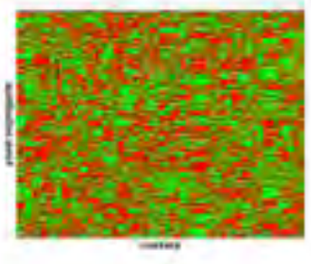


Yeast segregants

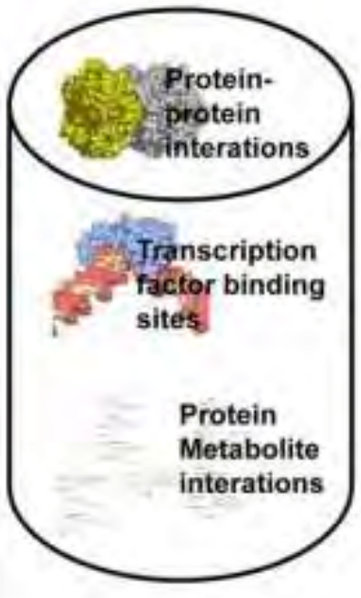
metabolites



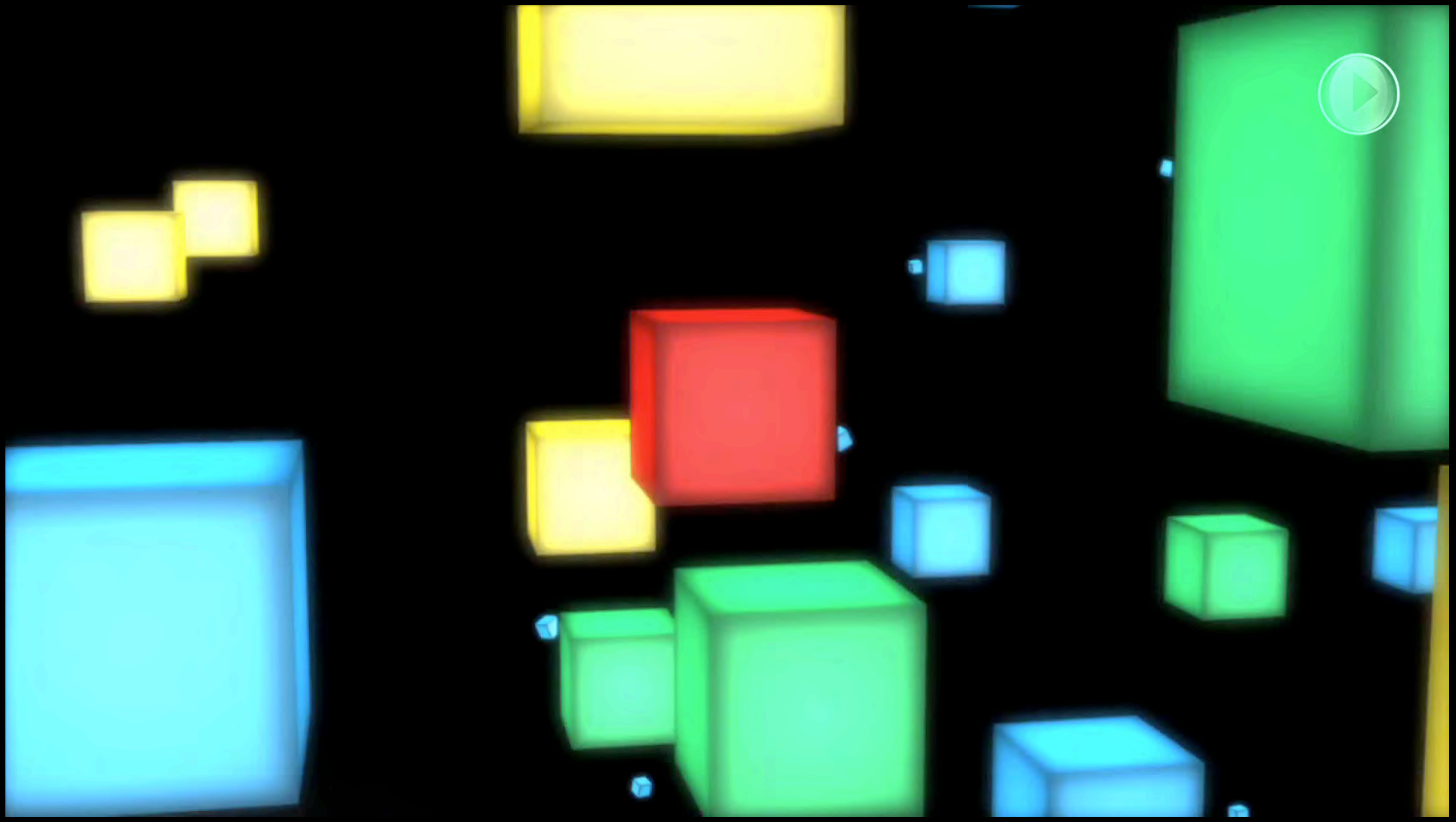
genotypes



Public databases



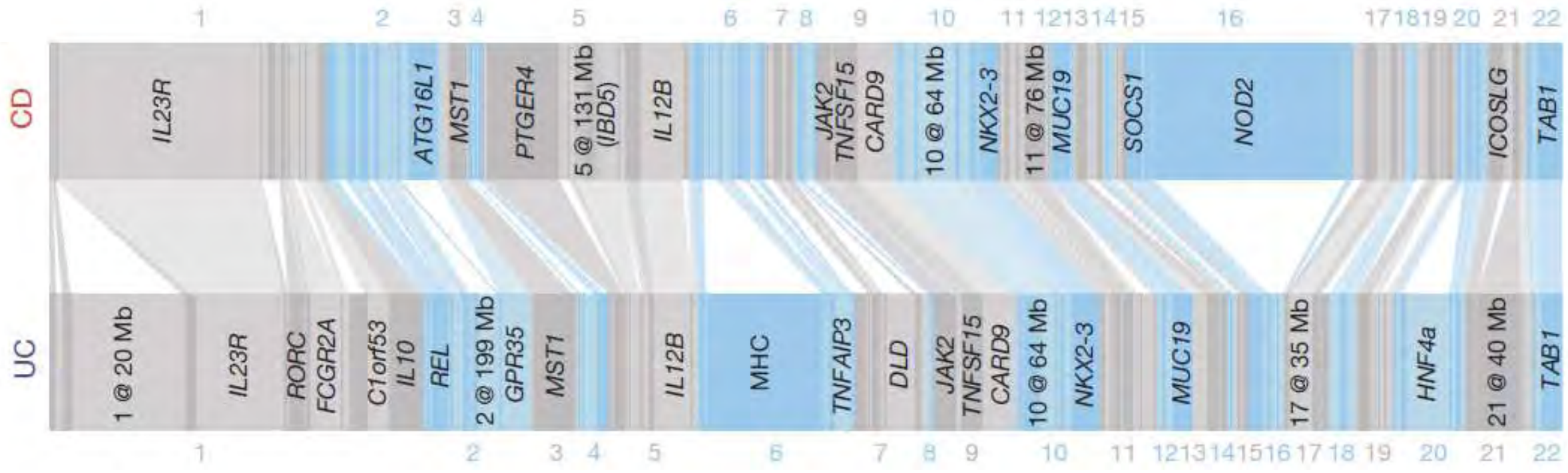
Slide courtesy of Eric Schadt



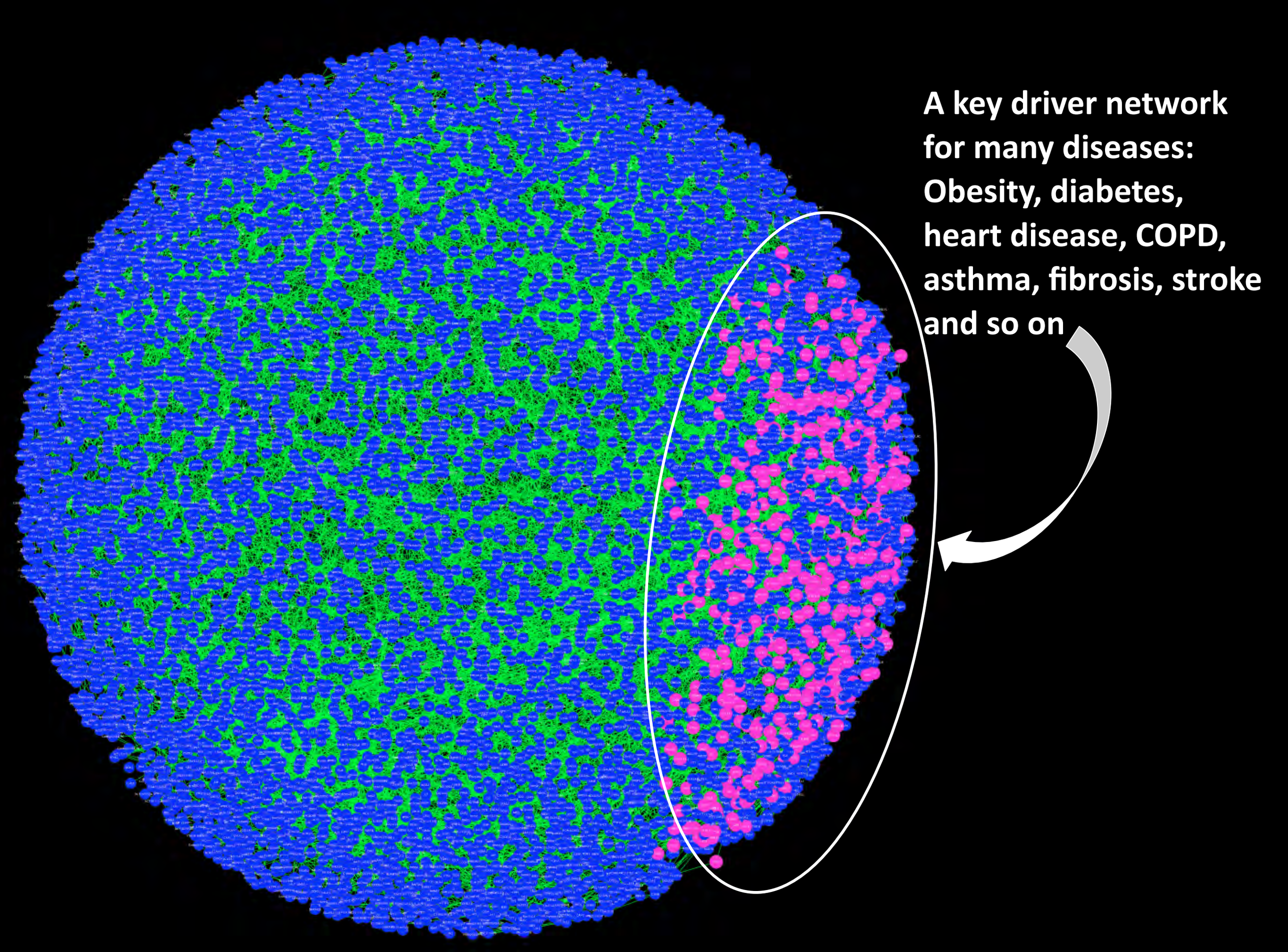
Organizing 163 genetic loci for IBD

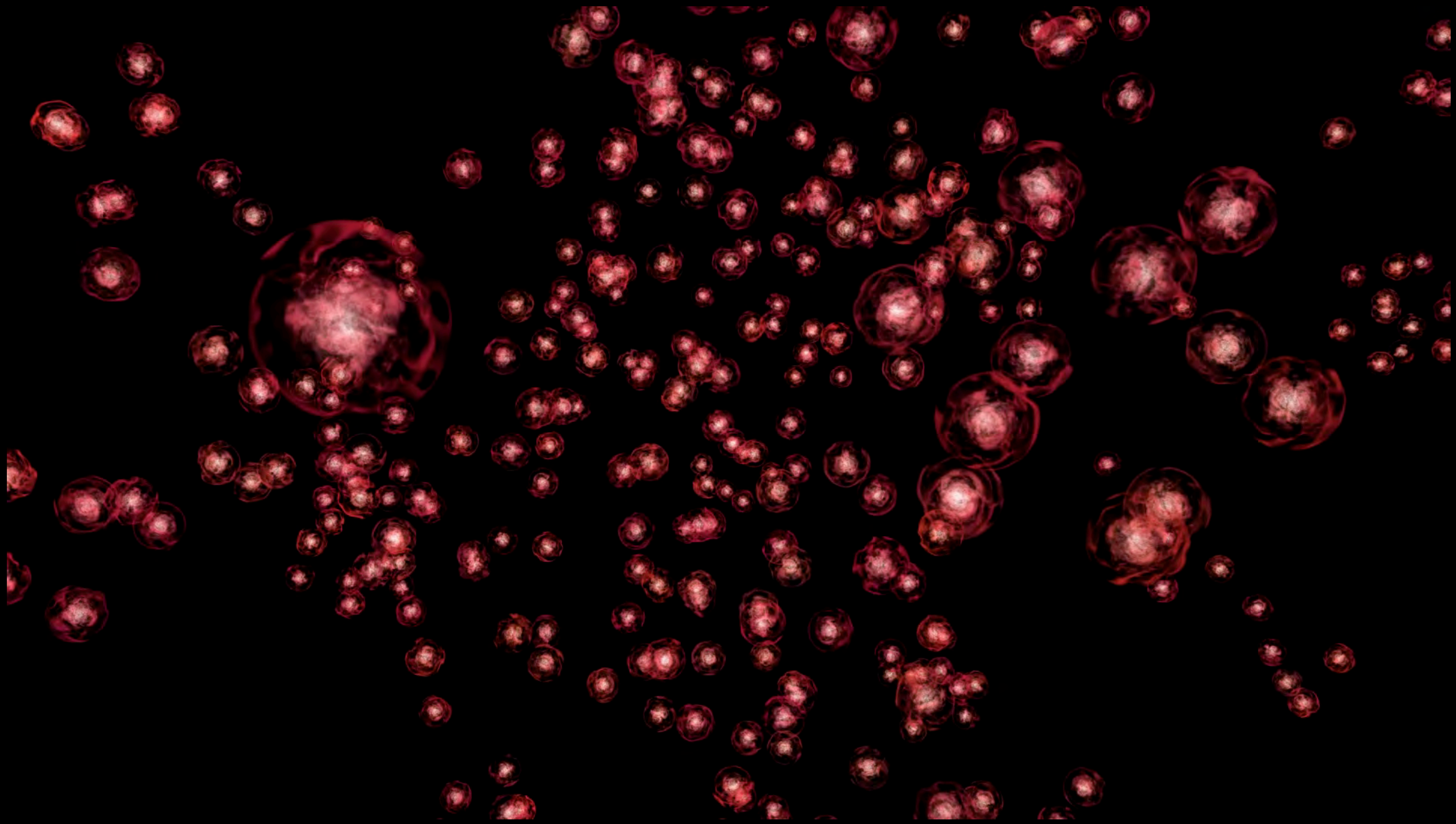
nature

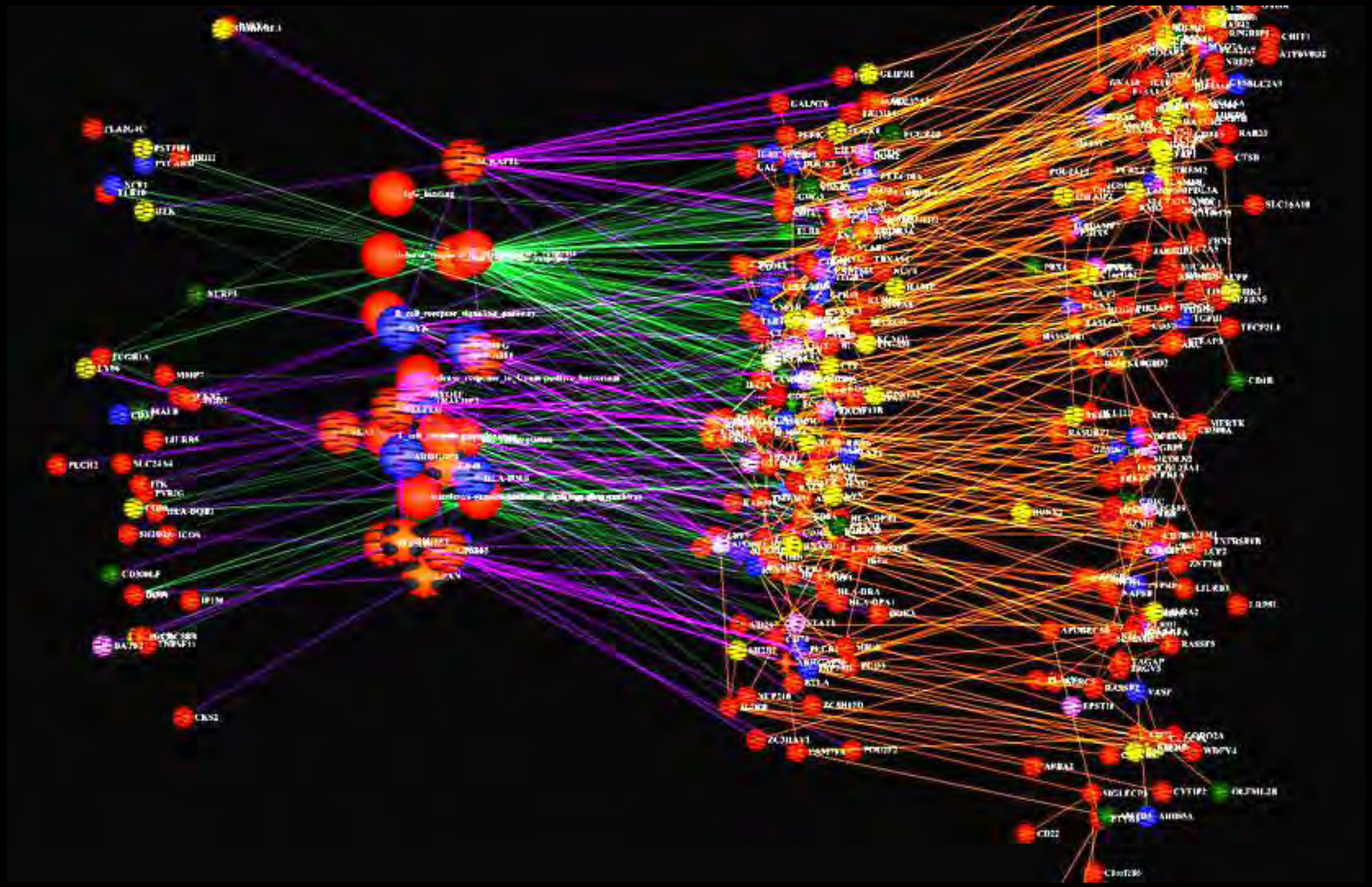
Host–microbe interactions have shaped the genetic architecture of inflammatory bowel disease



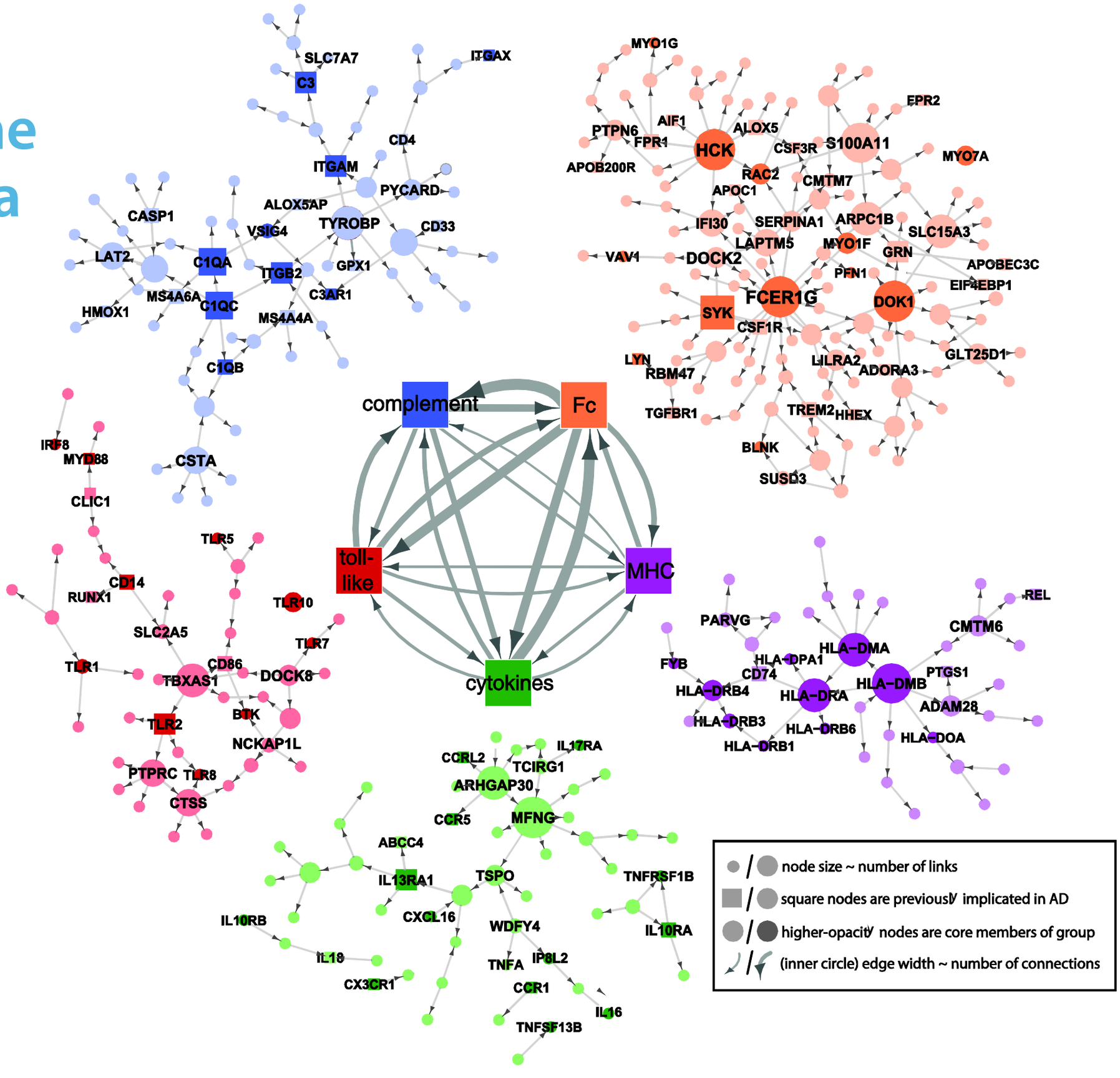
Problem: How do you make sense of 163 loci to understand a complex disease like IBD?


A key driver network
for many diseases:
Obesity, diabetes,
heart disease, COPD,
asthma, fibrosis, stroke
and so on





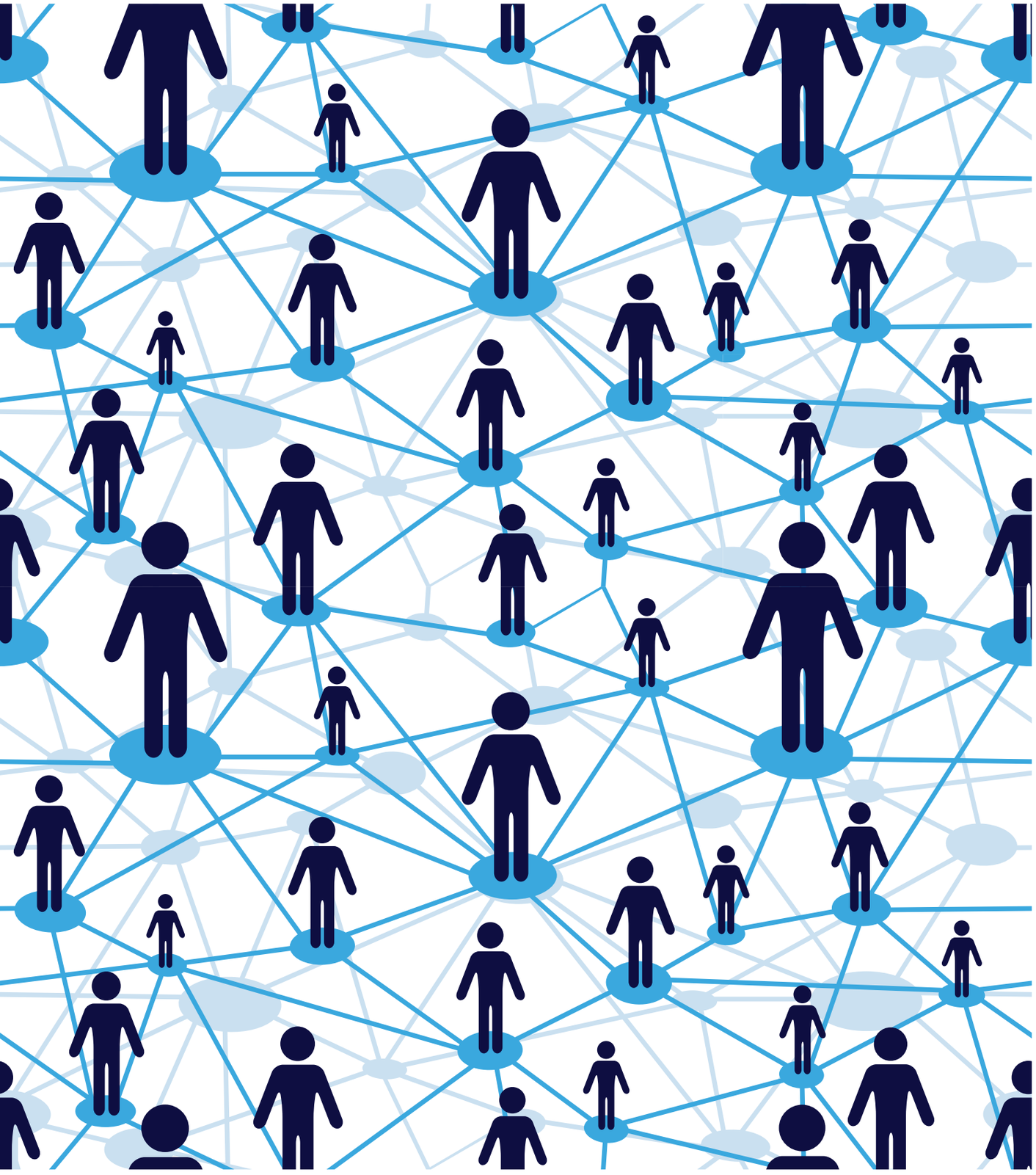
Alzheimer's neuro-immune and microglia network

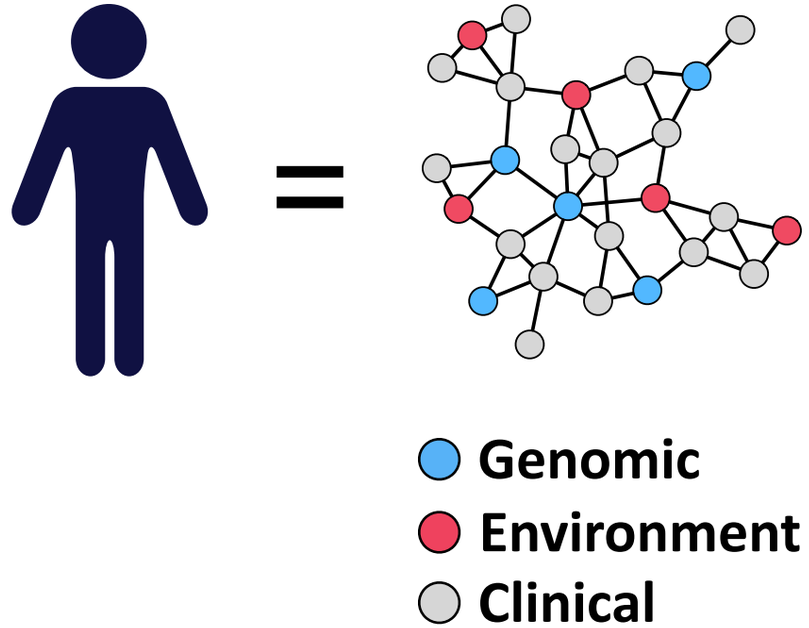


Bin Zhang, PhD

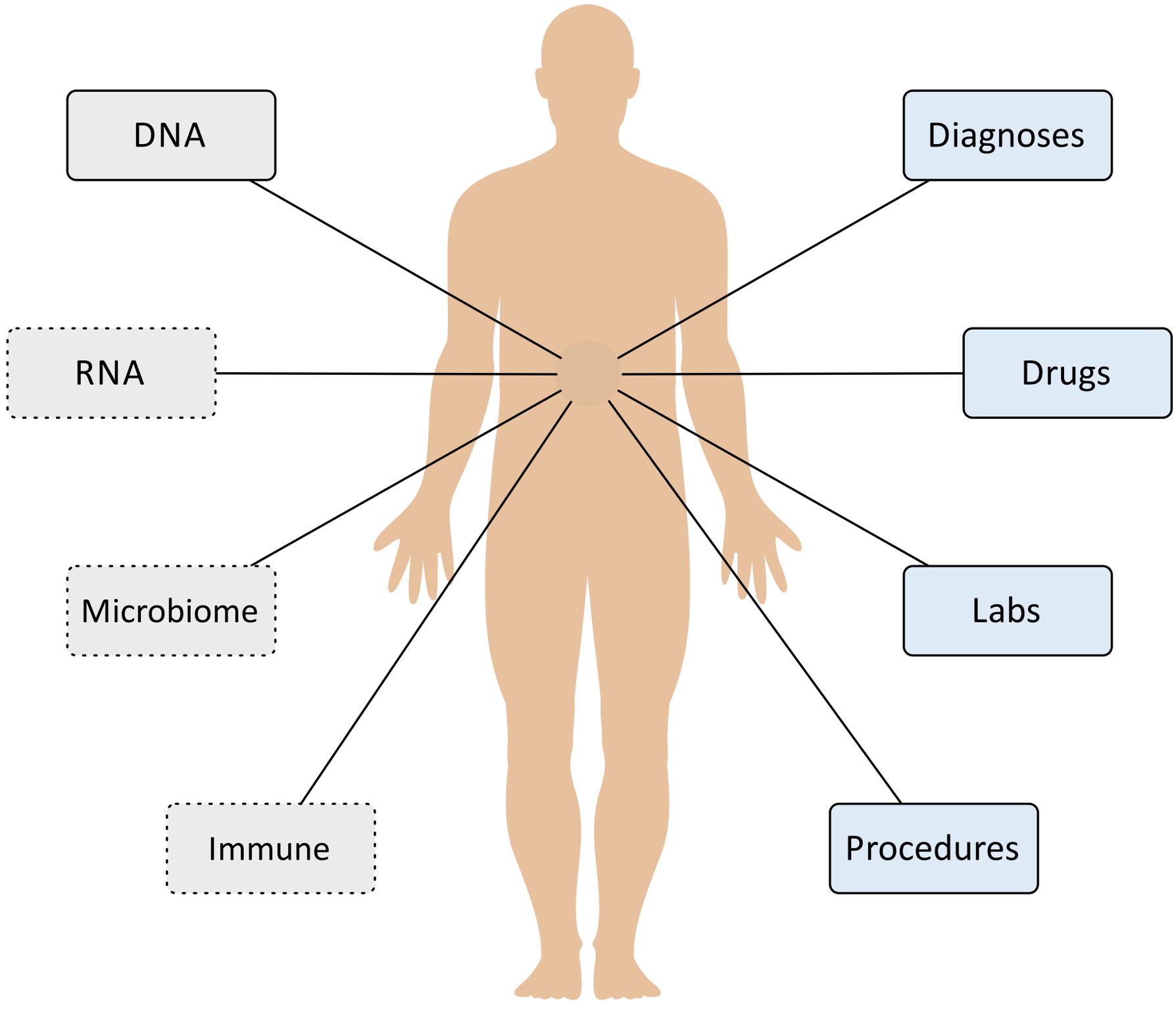
Zhang B *et al.* Tracing Multi-System Failure in Alzheimer Disease to Causal Genes. *Cell* 2013

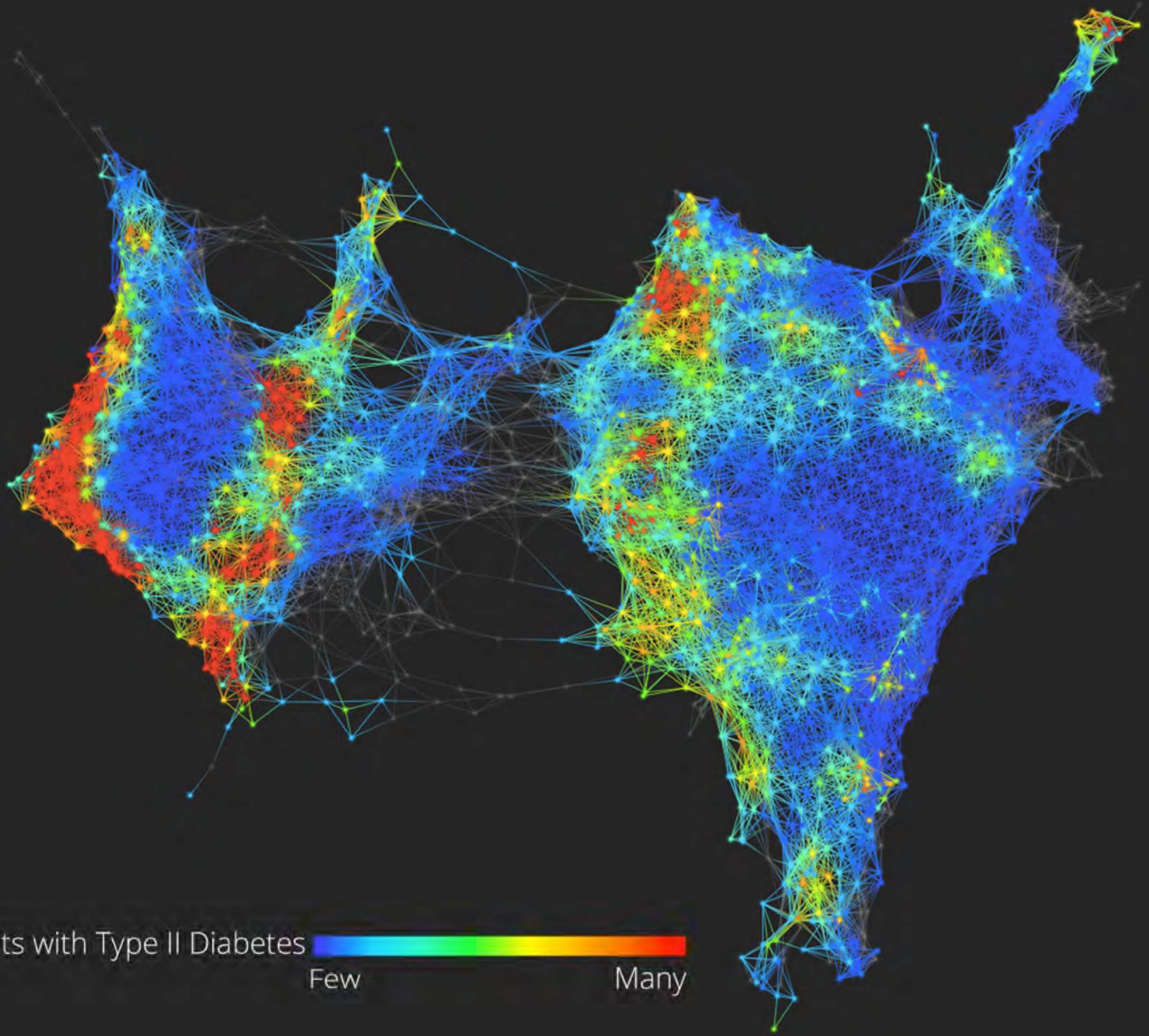
Understanding the multiscale complexity of patient populations





Capturing rich multi scale data on patients through the Mount Sinai Biobank




Patients with Type II Diabetes
Few
Many

Column Name	Cate...	...	...	p-value	...	...	CHROM	...	...	...	GENE	Entrez_id
1_152690546...	A|A	...	...	3.572E-6	...	...	1	...	...	...	CACNA1E	777
10_95069144...	A|C	...	...	5.04E-5	...	...	10	...	...	...	ENTPD7	57089
9_5494437_5...	C|C	...	...	5.183E-5	...	...	9	...	...	...	PDCD1LG2	80380
6_39386331_...	A|A	...	...	6.4E-5	...	...	6	...	...	...	KIF6	221458
1_1130726_1...	A|C	...	...	1.172E-4	...	...	1	...	...	...	C1orf222	339457
20_13677404...	G|G	...	...	1.446E-4	...	...	20	...	...	...	ESF1	51575
6_2546383_2...	T|T	...	...	1.465E-4	...	...	6	...	...	...	MYLK4	340156
4_97059593_...	C|C	...	...	1.539E-4	...	...	4	...	...	...	EMCN	51705
10_32745261...	C|T	...	...	1.622E-4	...	...	10	...	...	...	C10orf68	79741
10_91737944...	C|C	...	...	1.648E-4	...	...	10	...	...	...	OPALIN	93377
10_32804397...	A|G	...	...	1.807E-4	...	...	10	...	...	...	C10orf68	79741
10_24858389...	A|A	...	...	1.863E-4	...	...	10	...	...	...	PRTFDC1	56952

OPEN ACCESS Freely available online

PLoS one

CACNA1E Variants Affect Beta Cell Function in Patients with Newly Diagnosed Type 2 Diabetes. The Verona Newly Diagnosed Type 2 Diabetes Study (VNDS) 3

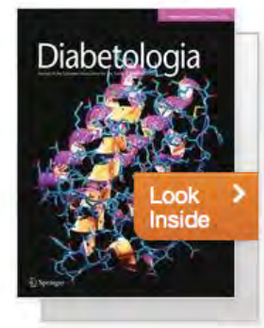
Maddalena Trombetta[1,2☯], Sara Bonetti[1*☯], MariaLinda Boselli[1], Fabiola Turrini[1], Giovanni Malerba[3], Elisabetta Trabetti[3], PierFranco Pignatti[3], Enzo Bonora[1,2], Riccardo C. Bonadonna[1,2*]

1 Department of Medicine, University of Verona, Verona, Italy, **2** Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy, **3** Department of Life and Reproduction Sciences, University of Verona, Verona, Italy

Diabetologia
December 2007, Volume 50, Issue 12, pp 2467-2475

Polymorphisms in the gene encoding the voltage-dependent Ca^{2+} channel $Ca_v2.3$ (*CACNA1E*) are associated with type 2 diabetes and impaired insulin secretion

J. Holmkvist, D. Tojjar, P. Almgren, V. Lyssenko, C. M. Lindgren, B. Isomaa, T. Tuomi, G. Berglund, E. Renström, L. Groop

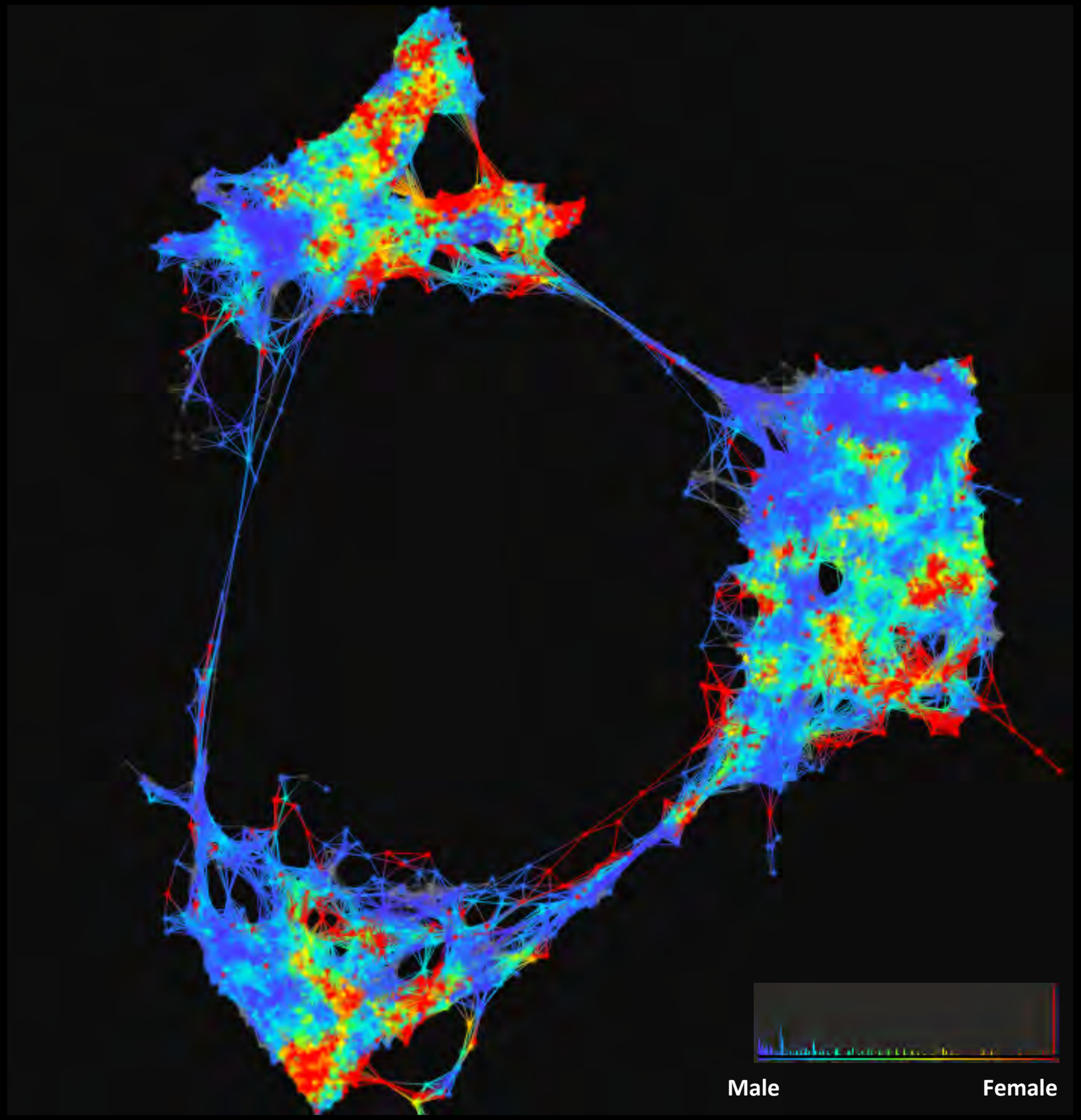


Patients with Type II Diabetes

Few — Many

Image credit:
Li Li (ISMMS)

Type 2, Type 3, and Type 4 diabetes?



“The future is already here — it's just not very evenly distributed”.

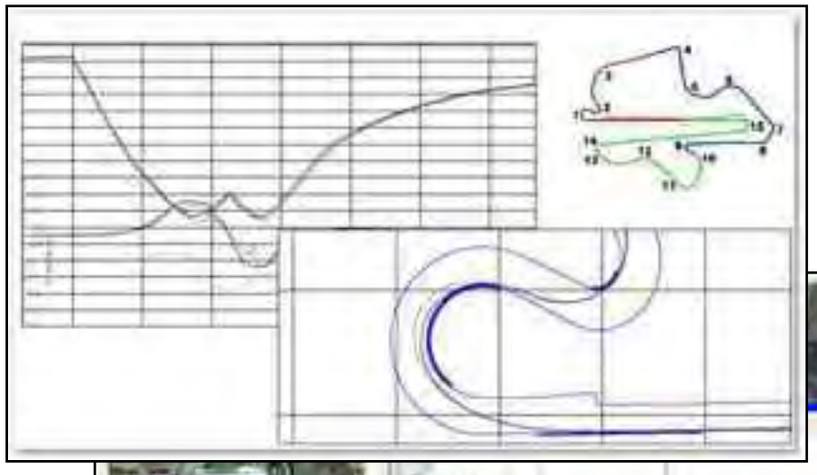
- William Gibson

200

Data Feeds

5Gb

Data/lap



300

Sensors

3,000

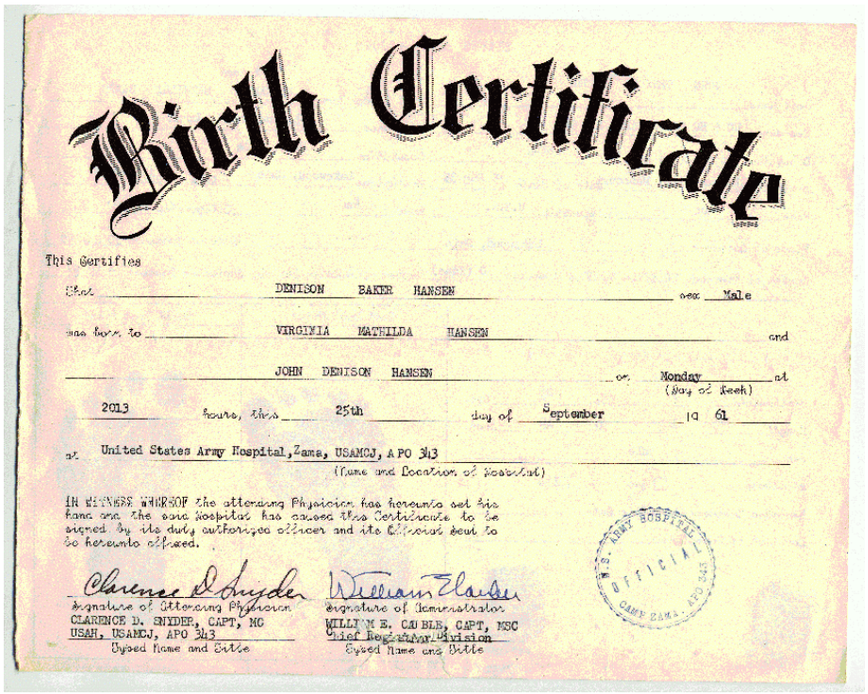
Variables/0.1 sec

>200Gb

Data/day

© Francois Chevalier

SIGN					
	0	1	2	1 min	5 min
Heart Rate	Absent	Less Than 100	Over 100	2	2
Respiratory Effort	Absent	Slow, Irregular	Good Cry	1	2
Muscle Tone	Limp	Some Flexion	Active Motion	1	2
Reflex Irritability	No Response	Grimace	Cry	1	2
Color	Pale	Body Pink, Extr. Blue	All Pink	1	2
TOTAL SCORE				6	10



Birth Certificate

This Certifies

That DENISON BAKER HANSEN was Male

was born to VIRGINIA MATHILDA HANSEN and

JOHN DENISON HANSEN on Monday (Day of Week) at

2013 hours, this 25th day of September 19 61

at United States Army Hospital, Zama, USAMCJ, APO 343
(Name and Location of Hospital)

IN WITNESS WHEREOF the attending Physician has hereunto set his hand and the said Hospital has caused this Certificate to be signed by its duly authorized officer and its Official Seal to be hereunto affixed.

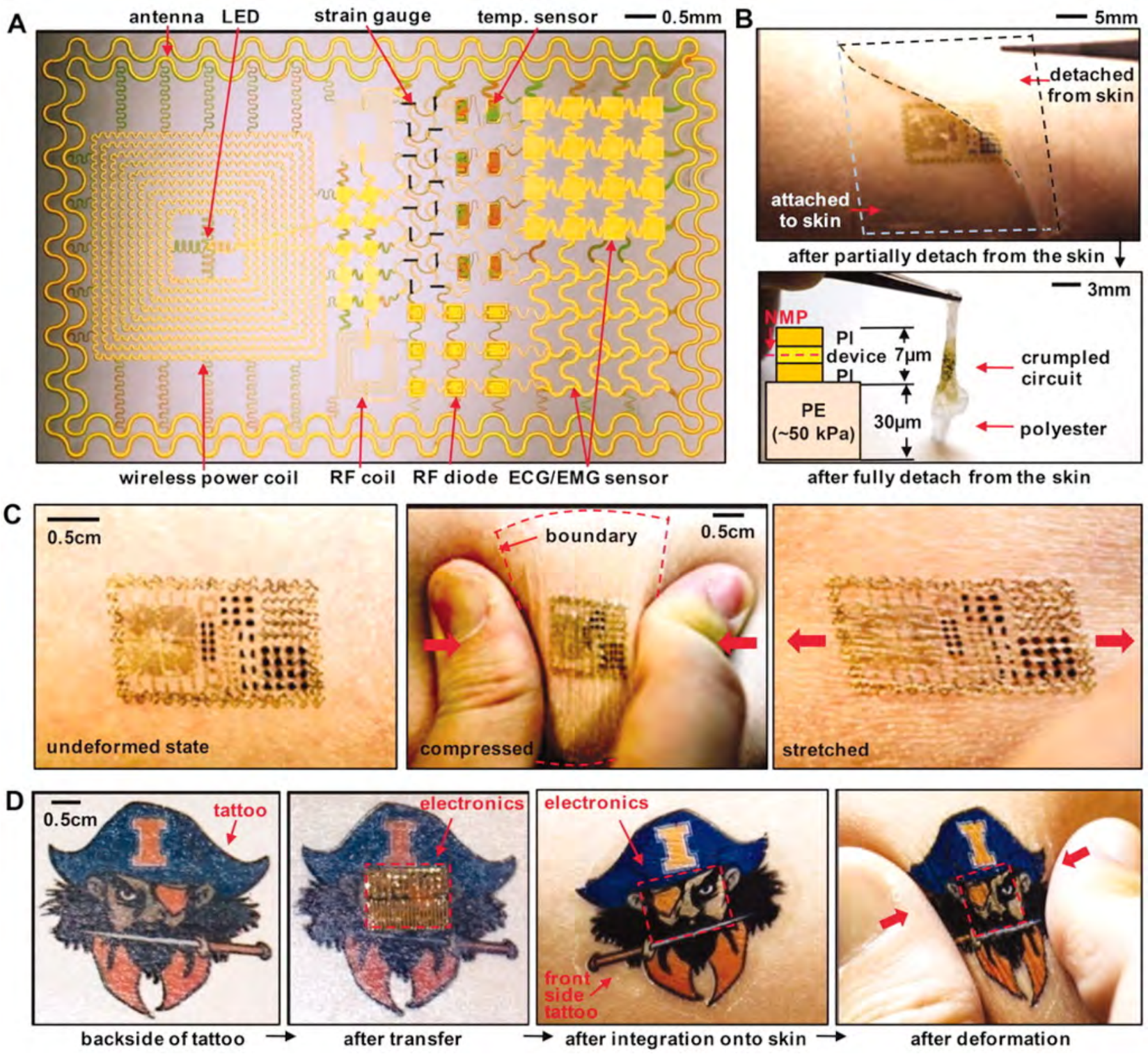
Clarence D. Snyder
Signature of Attending Physician
CLARENCE D. SNYDER, CAPT, MC
USAH, USAMCJ, APO 343
Typed Name and Title

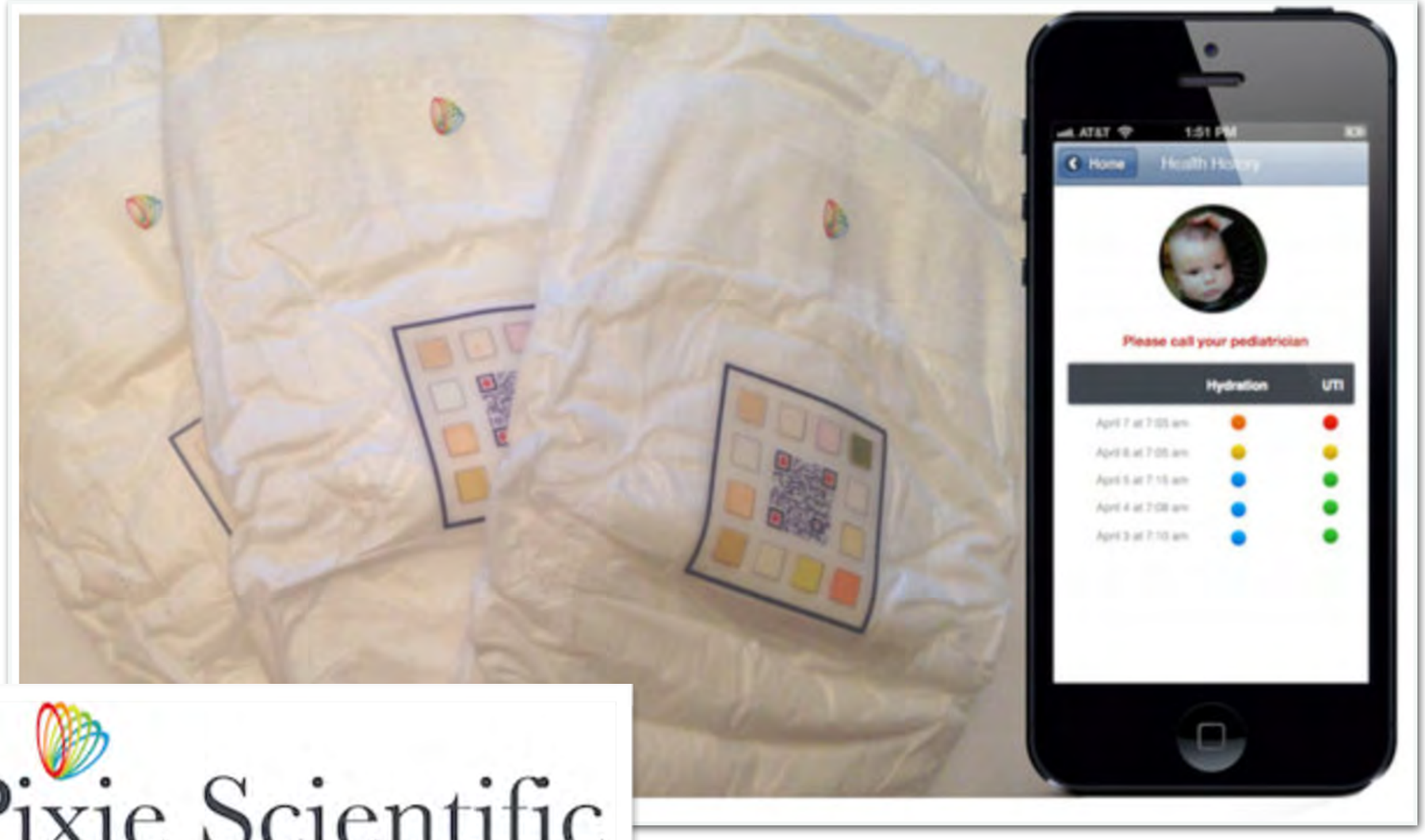
William E. Cauble
Signature of Administrator
WILLIAM E. CAUBLE, CAPT, MSC
Chief Registration Division
Typed Name and Title

U.S. ARMY HOSPITAL OFFICIAL SEAL CAMP ZAMA, APO 343

We are on the crest of a tsunami in consumer sensor technologies

Printable tattoo biosensor





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Feel better, have more energy & find out what's going on inside your body - quickly and conveniently. Spend more time doing what you love, less time at the doctor.

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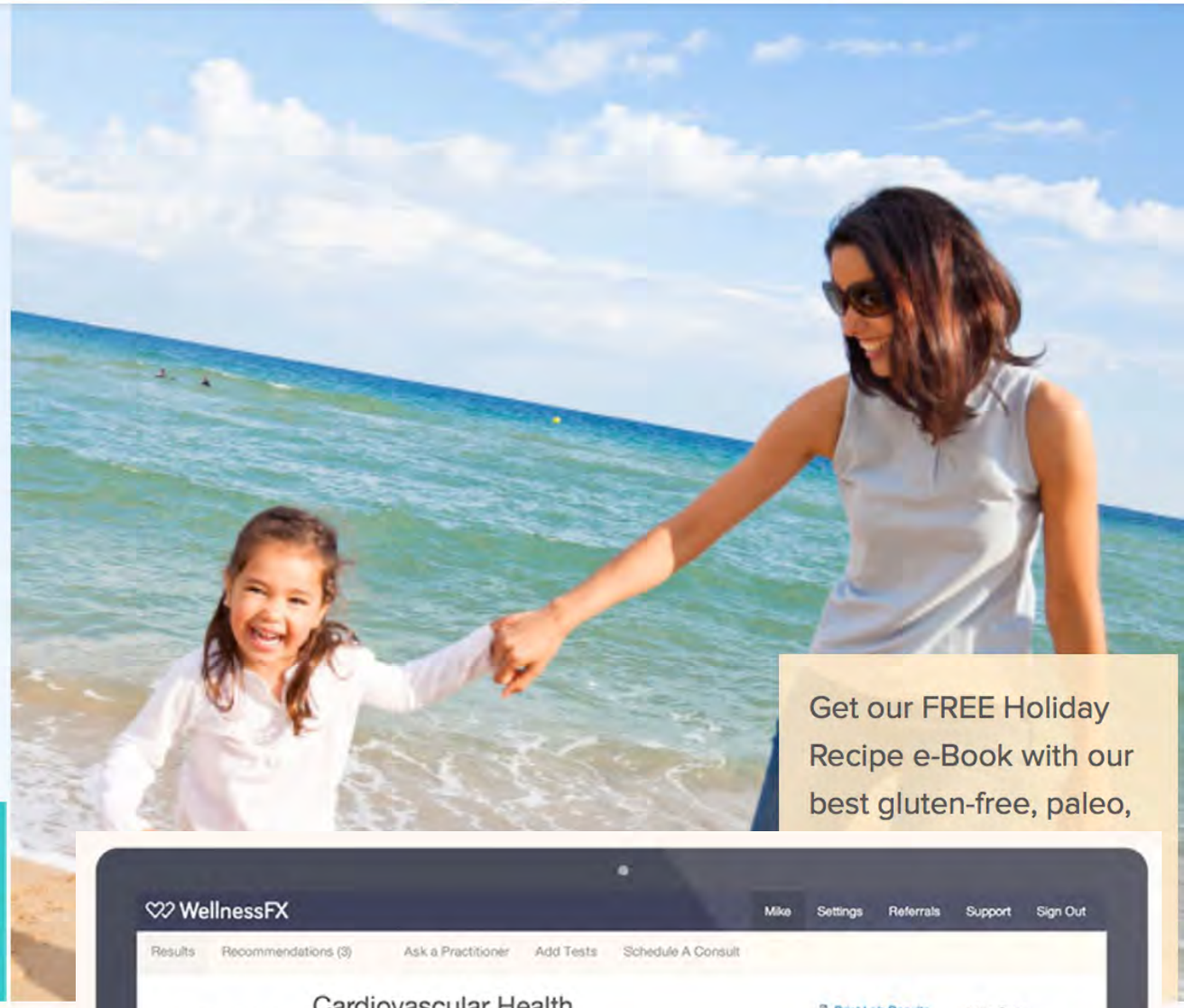


Get our FREE Holiday Recipe e-Book with our best gluten-free, paleo,

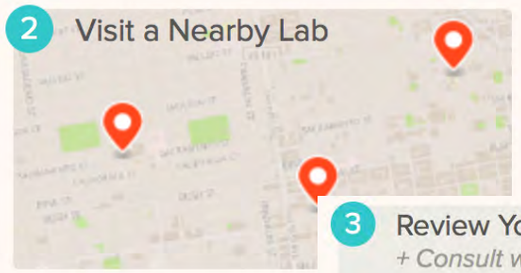
Own Your Health

Lose Weight or Gain Energy

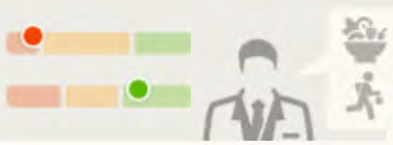
Optimize Your Performance

Check Health Risks

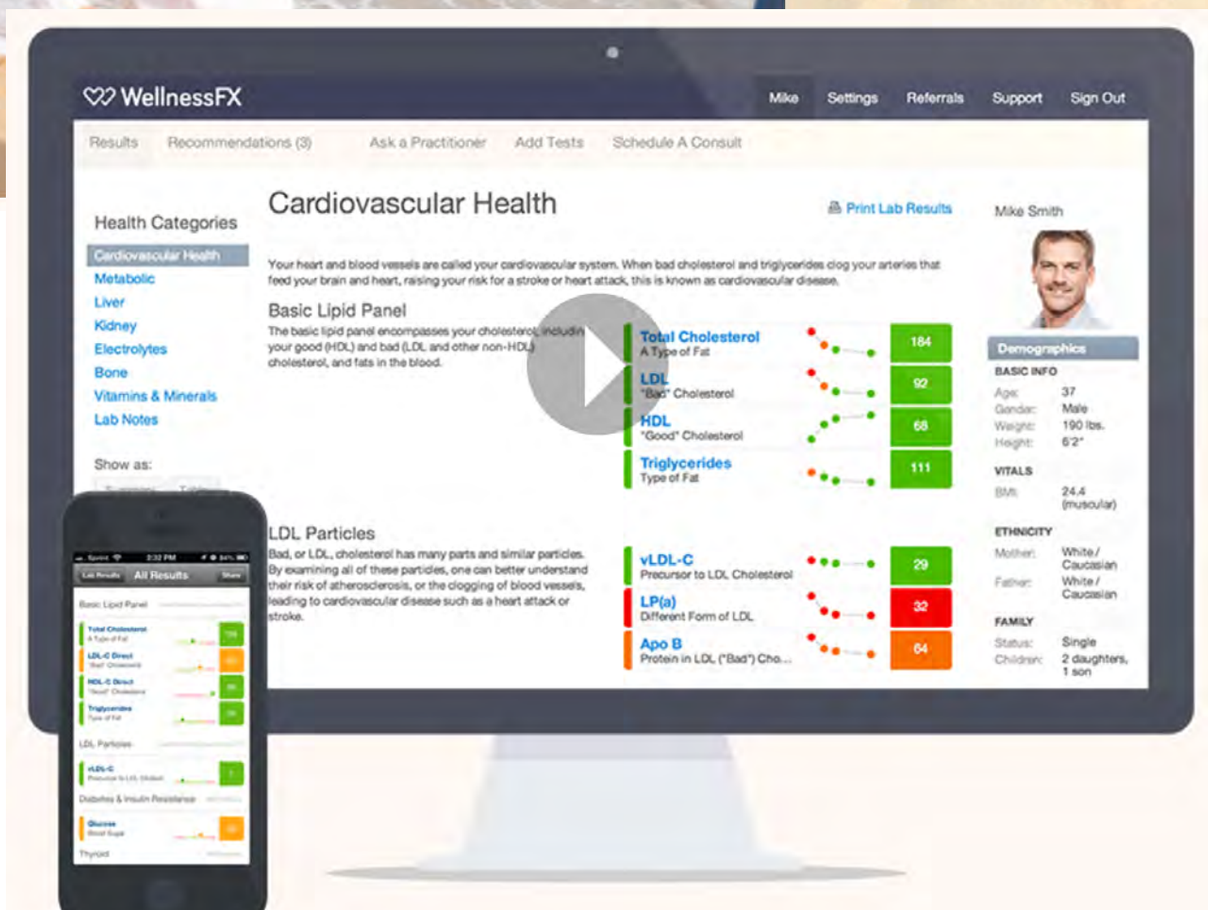
2 Visit a Nearby Lab



3 Review Your Lab Results
*+ Consult with an Expert**



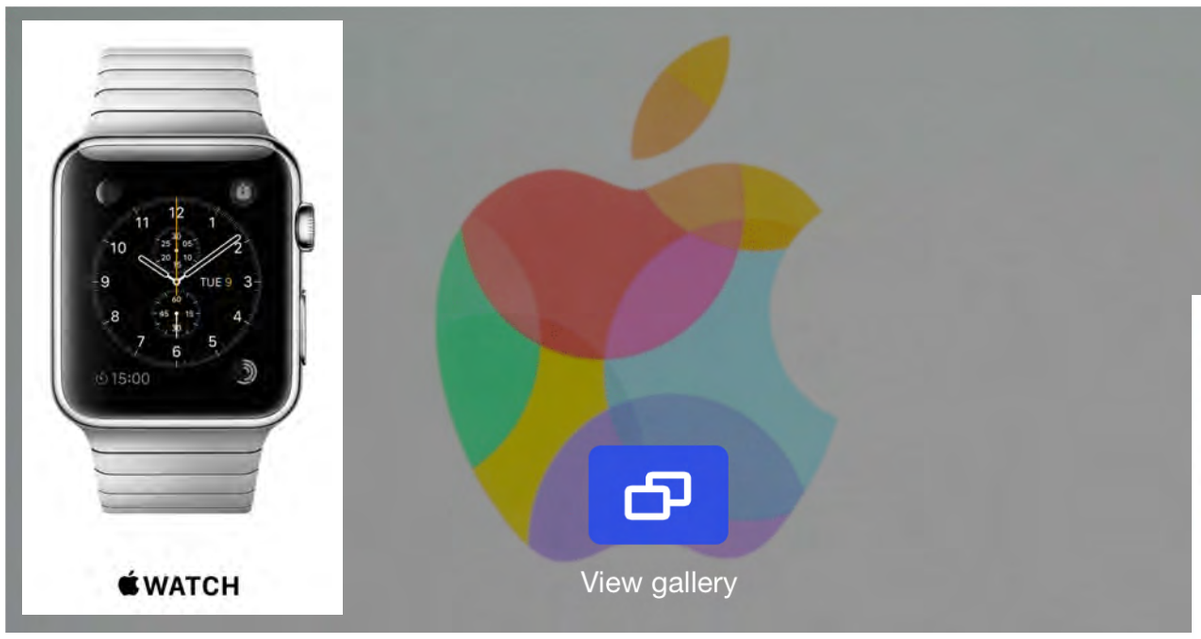
4 Improve and Retest



Consumer health tools as a driver of data-driven healthcare

Apple's iWatch Project Is Starting To Sound Incredible: They're Hiring Experts In Blood Monitoring

BUSINESS INSIDER By **Jay Yarow**
3 hours ago



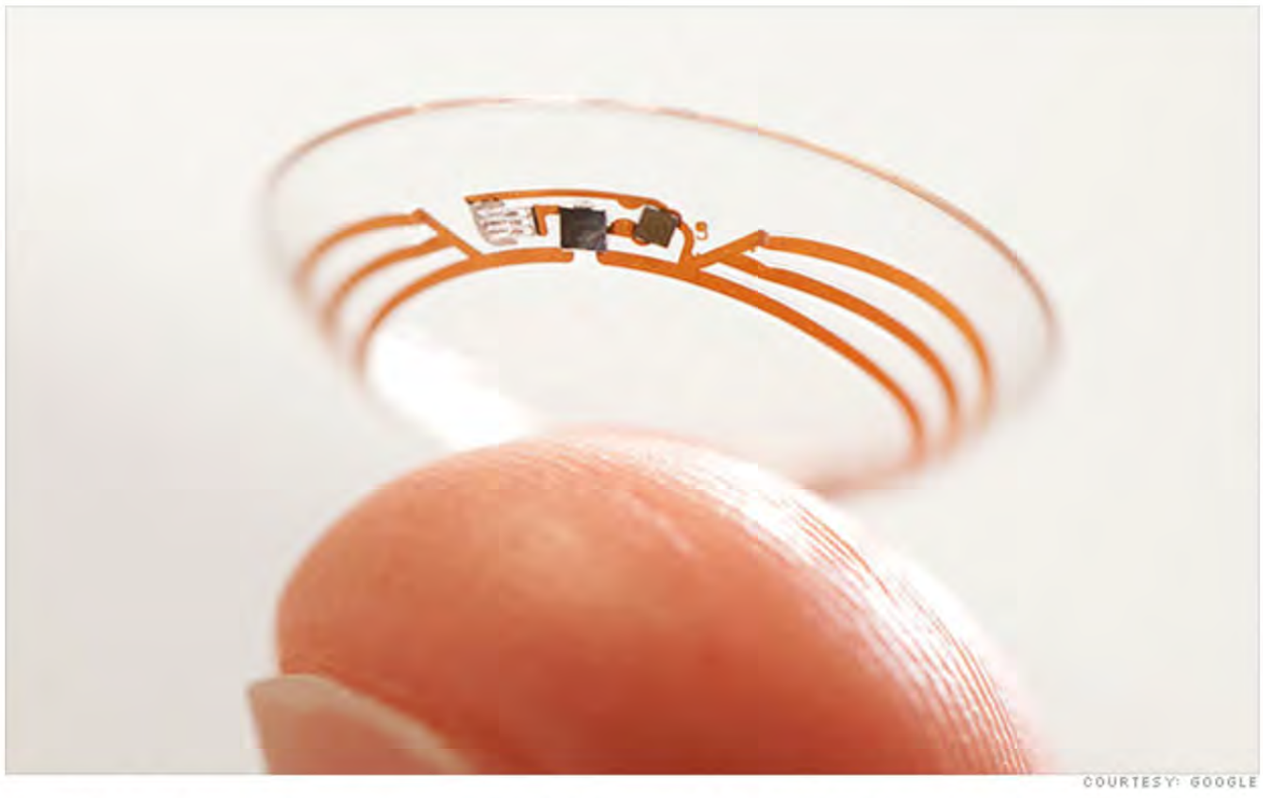
Where will most of the health data be in 5-10 years?

Google to make smart contact lenses

CNNMoney

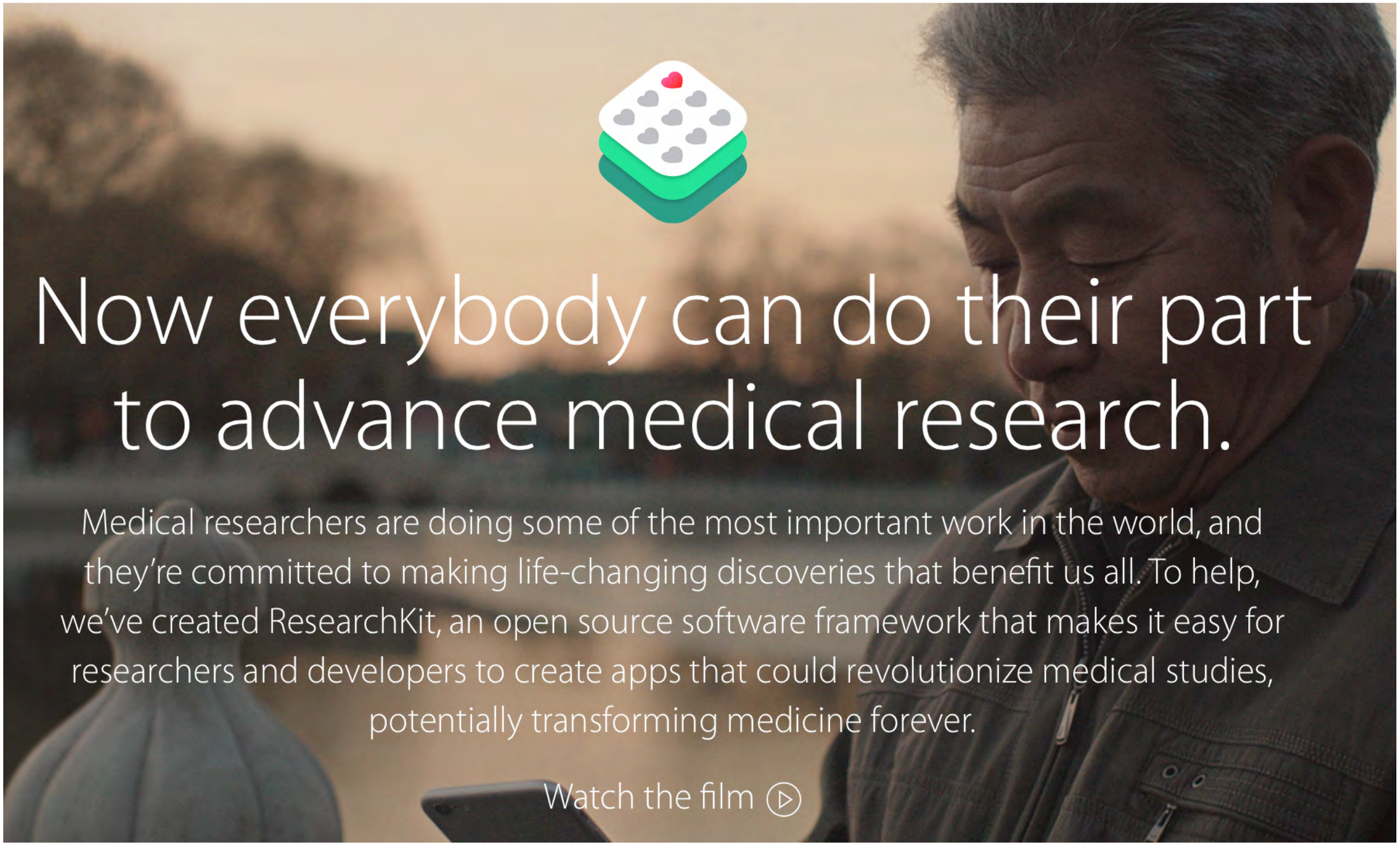
By David Goldman @DavidGoldmanCNN January 17, 2014: 7:47 AM ET

Recommend 12k

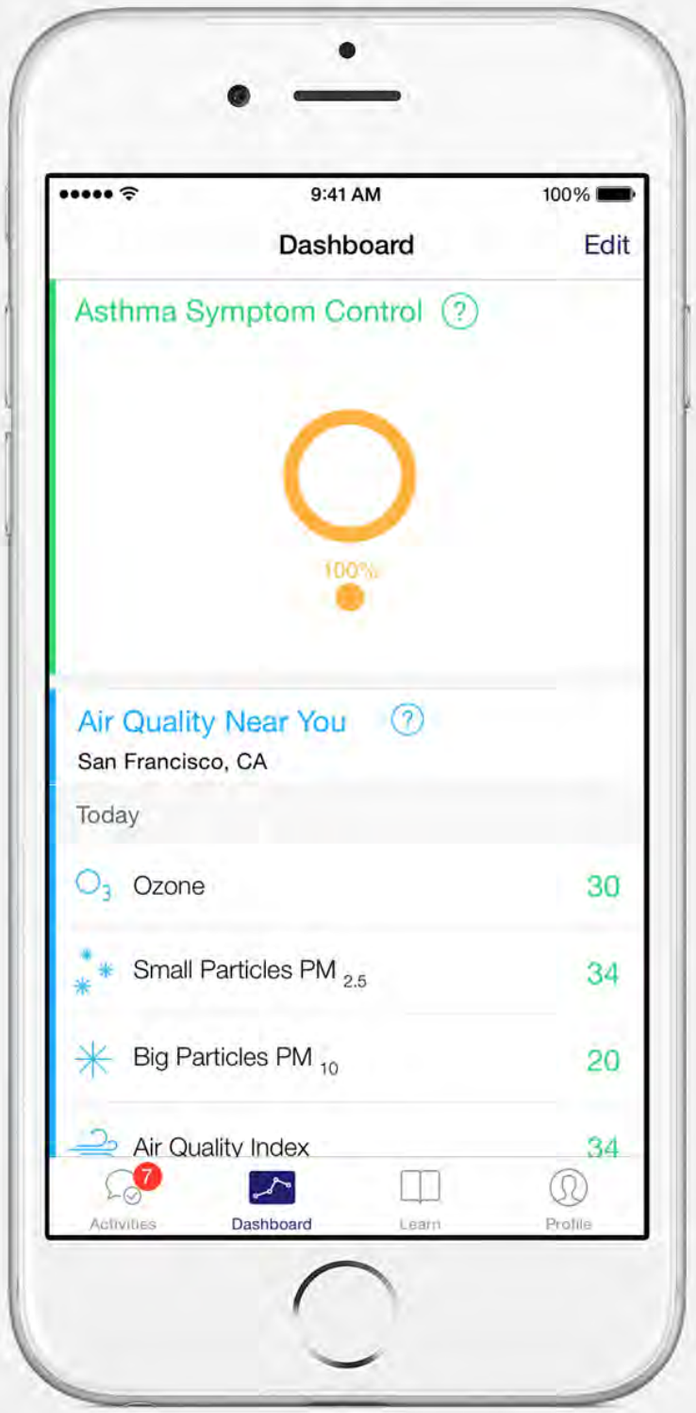


Google is developing smart contact lenses that will measure diabetics' blood glucose levels.

Electronic Consent and Patient Engagement



Electronic Consent and Patient Engagement



Helping asthma sufferers breathe more easily.

Mount Sinai, Weill Cornell Medical College, and LifeMap developed their Asthma Health app to gain greater insight into triggers for the disease. It helps participants self-manage their asthma by avoiding areas where air quality could worsen symptoms. And since the study tracks symptom patterns in individuals, researchers hope to discover new ways to personalize treatment.

Asthma Health
Mount Sinai, Weill Cornell Medical College, and LifeMap
View in the App Store ›

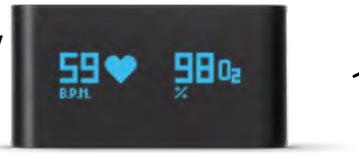
Data from the GPS in your iPhone is combined with information about the air quality in your city to help you avoid areas where symptoms could be triggered.

A Learning Digital Health Platform for Chronic Lung Disease

Environmental/
Geospatial data

Real-time learning on
patient population data

Inhaler



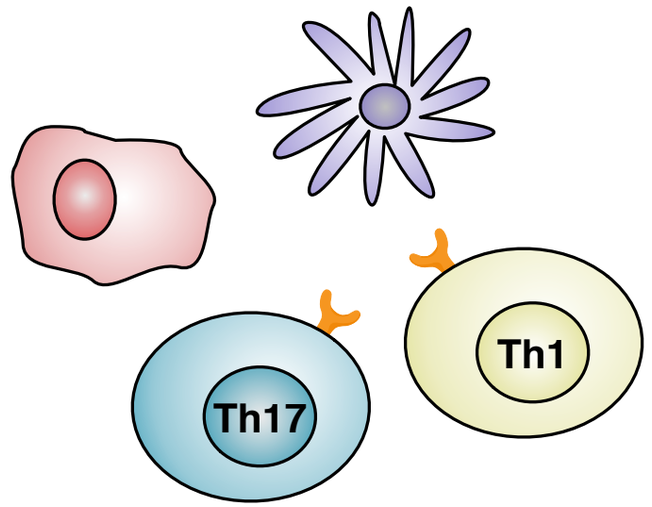
Activity/
Vitals

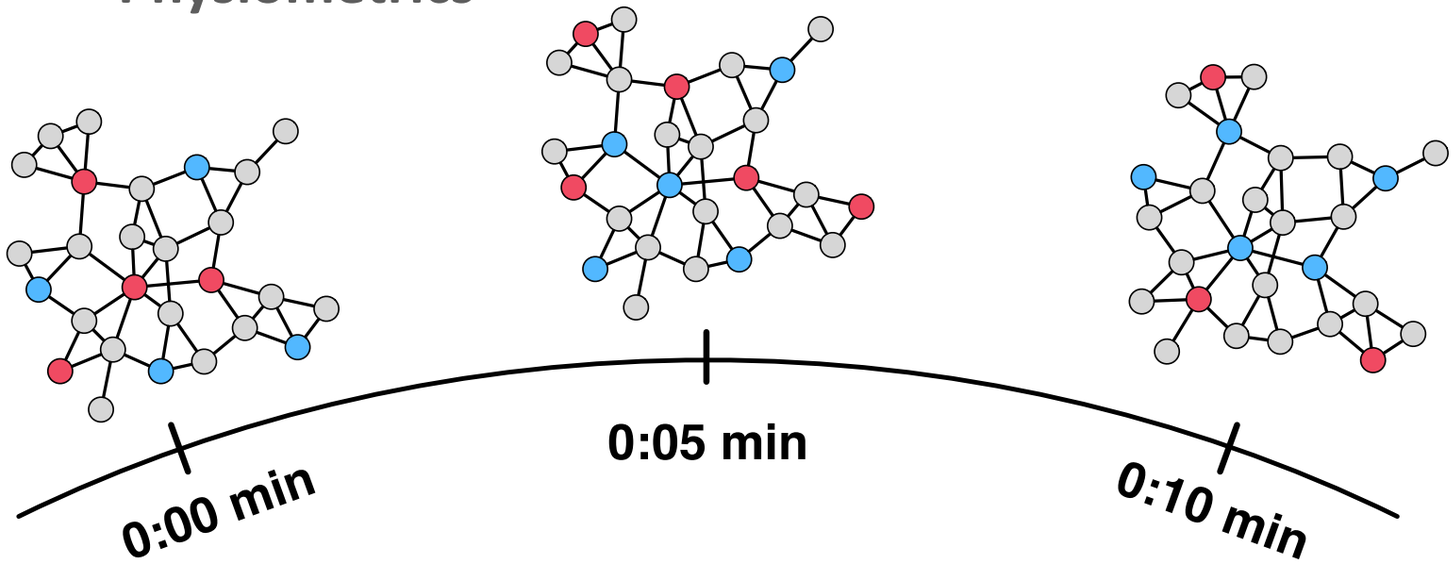
Spirometry

Actionable insights
delivered to EMR
at point-of-care

Personalized multiscale networks to model dynamics of complex disease

DNA
Cell-specific RNA
Cytokines
Clinical labs
Mobile devices
Microbiome
Physiometrics





In the future you will have coordinates instead of a diagnosis

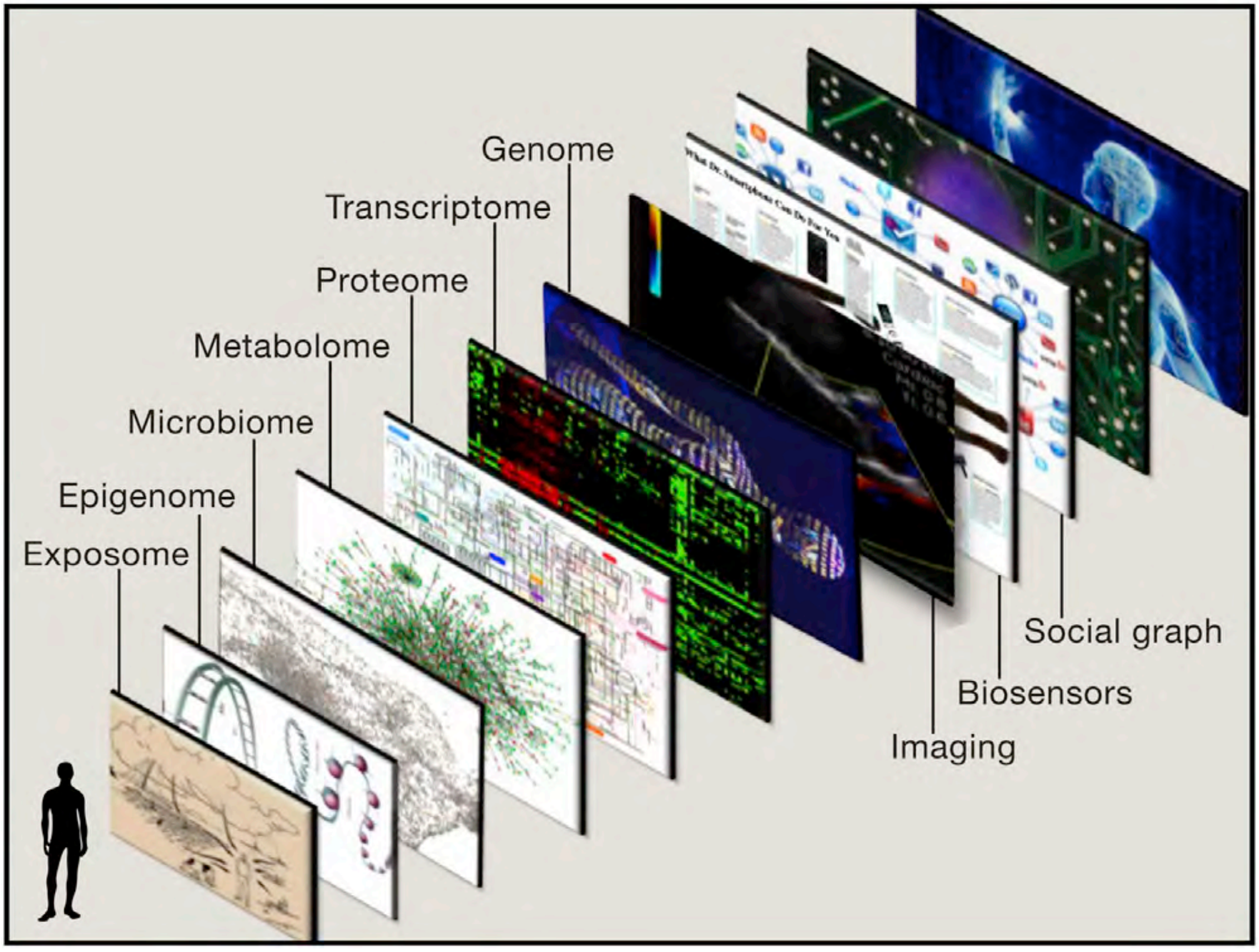


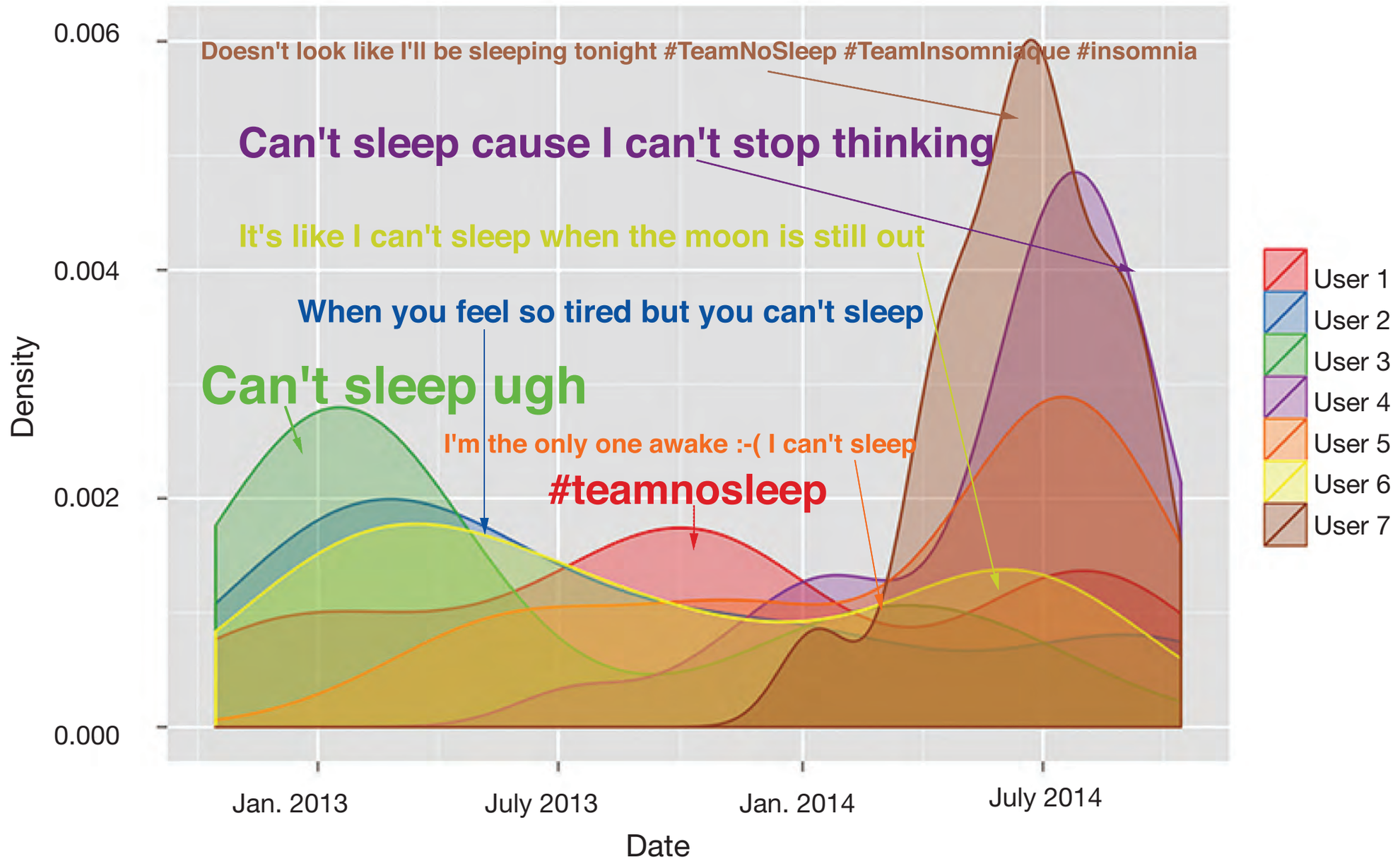
Figure 1. Geographic Information System of a Human Being

Topol EJ. Individualized Medicine from Prewomb to Tomb *Cell* 157, March 27, 2014

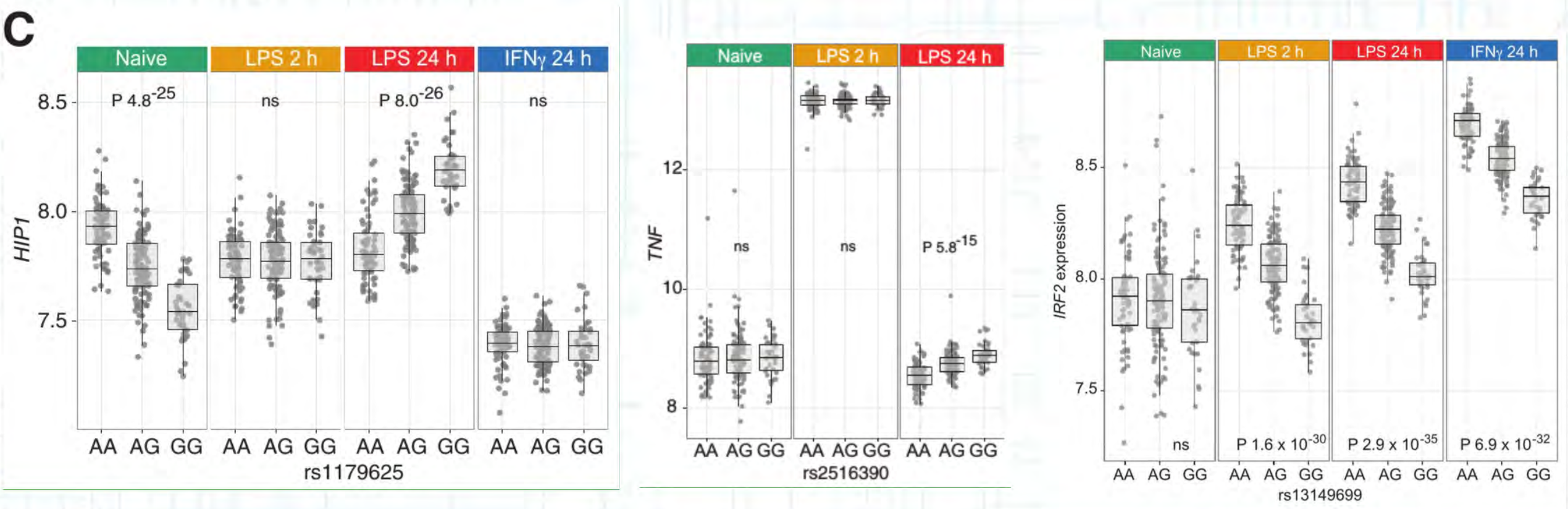
We can embrace digital health and sensors to map the human phoneme and envirome

The digital phenotype

Sachin H Jain, Brian W Powers, Jared B Hawkins & John S Brownstein



It's all about context



Innate Immune Activity Conditions the Effect of Regulatory Variants upon Monocyte Gene Expression

Benjamin P. Fairfax,[1]* Peter Humburg,[1]† Seiko Makino,[1]† Vivek Naranbhai,[1] Daniel Wong,[1] Evelyn Lau,[1] Luke Jostins,[1] Katharine Plant,[1] Robert Andrews,[2] Chris McGee,[2] Julian C. Knight[1]*

SCIENCE VOL 343 7 MARCH 2014

The emergence of science- and data-driven wellness

info@precisionwellness.org

The emergence of science- and data-driven wellness

Digital Health

Data Science

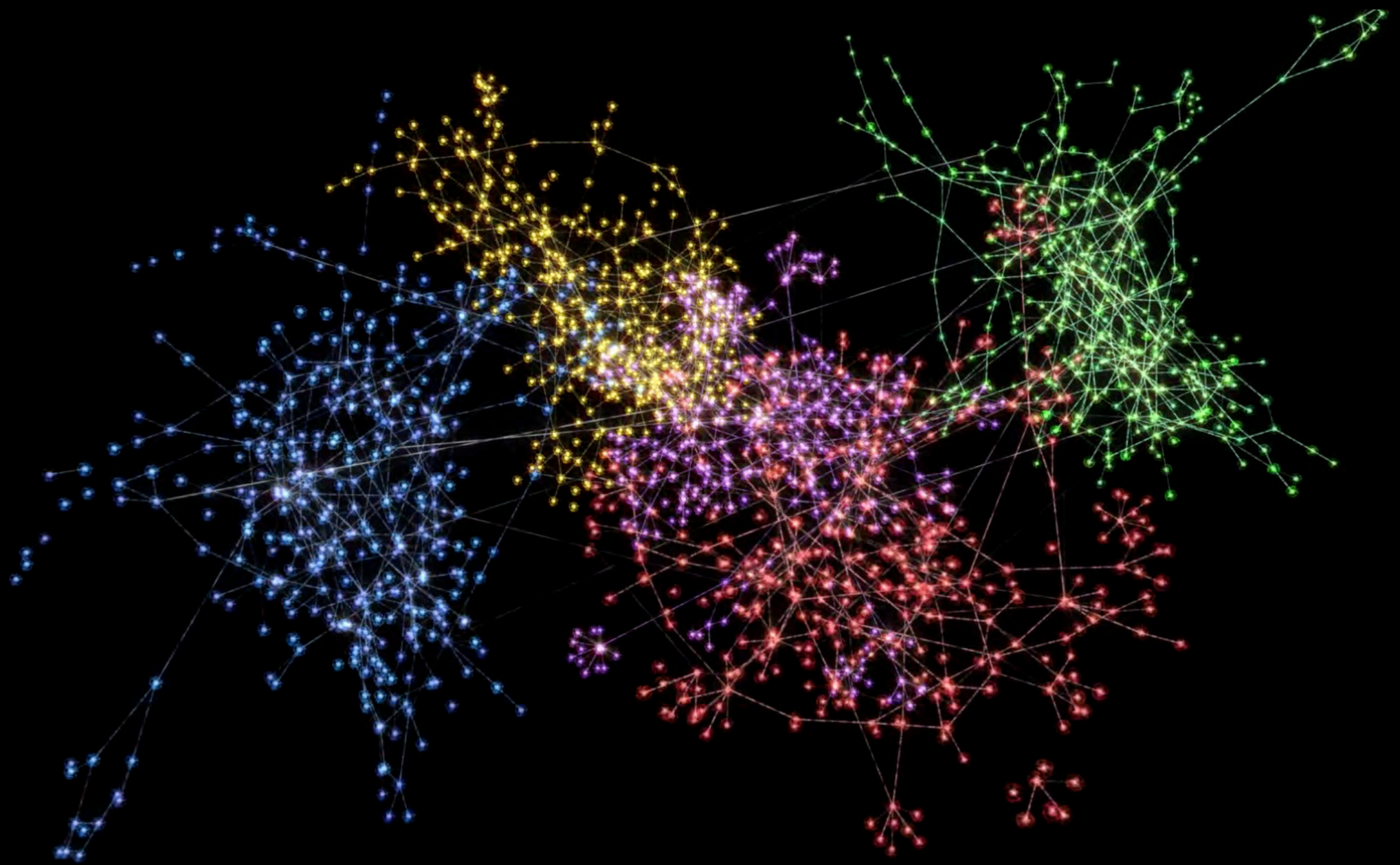
Molecular Profiling

Clinical Medicine

The Harris Center for Precision Wellness

info@precisionwellness.org

www.precisionwellness.org



Who are the resilient among us?

Icahn School of Medicine at Mount Sinai

The Resilience Project:

A Search for Unexpected Heroes

Sage BIONETWORKS

The Science Resilience Test Kit What You Get Back Register Now

You can donate your DNA to medical research as we search for "healthy" adults who have rare genetic changes that we'd expect to cause severe illness in childhood. We know that these "resilient" people exist, and we believe if we can understand what is protecting them from illness, then we can make advances towards treating or even preventing these diseases.

Listen now: TED Talk 2014

http://resilienceproject.me

Web-scale deep computing as the future of medicine and research

Google computer works out how to spot cats

A Google research team has trained a network of 1,000 computers wired up like a brain to recognise cats.

The team built a neural network, which mimics the working of a biological brain, that worked out how to spot pictures of cats in just three days.

The cat-spotting computer was created as part of a larger project to investigate machine learning.

Millions of images were used to train the neural network

Google is planning to use the learning system to help with its indexing systems and with language translation.

BBC

http://www.bbc.com/news/technology-18595351

Web-scale deep computing as the future of medicine and research

Science

AAAS

The human splicing code reveals new insights into the genetic determinants of disease

Hui Y. Xiong,* Babak Alipanahi,* Leo J. Lee,* Hannes Bretschneider, Daniele Merico, Ryan K. C. Yuen, Yimin Hua, Serge Gueroussov, Hamed S. Najafabadi, Timothy R. Hughes, Quaid Morris, Yoseph Barash, Adrian R. Krainer, Nebojsa Jojic, Stephen W. Scherer, Benjamin J. Blencowe, Brendan J. Frey†

Xiong et al. Science 9 January 2015

Thank you for your attention

Email: joel.dudley@mssm.edu

Twitter: @jdudley

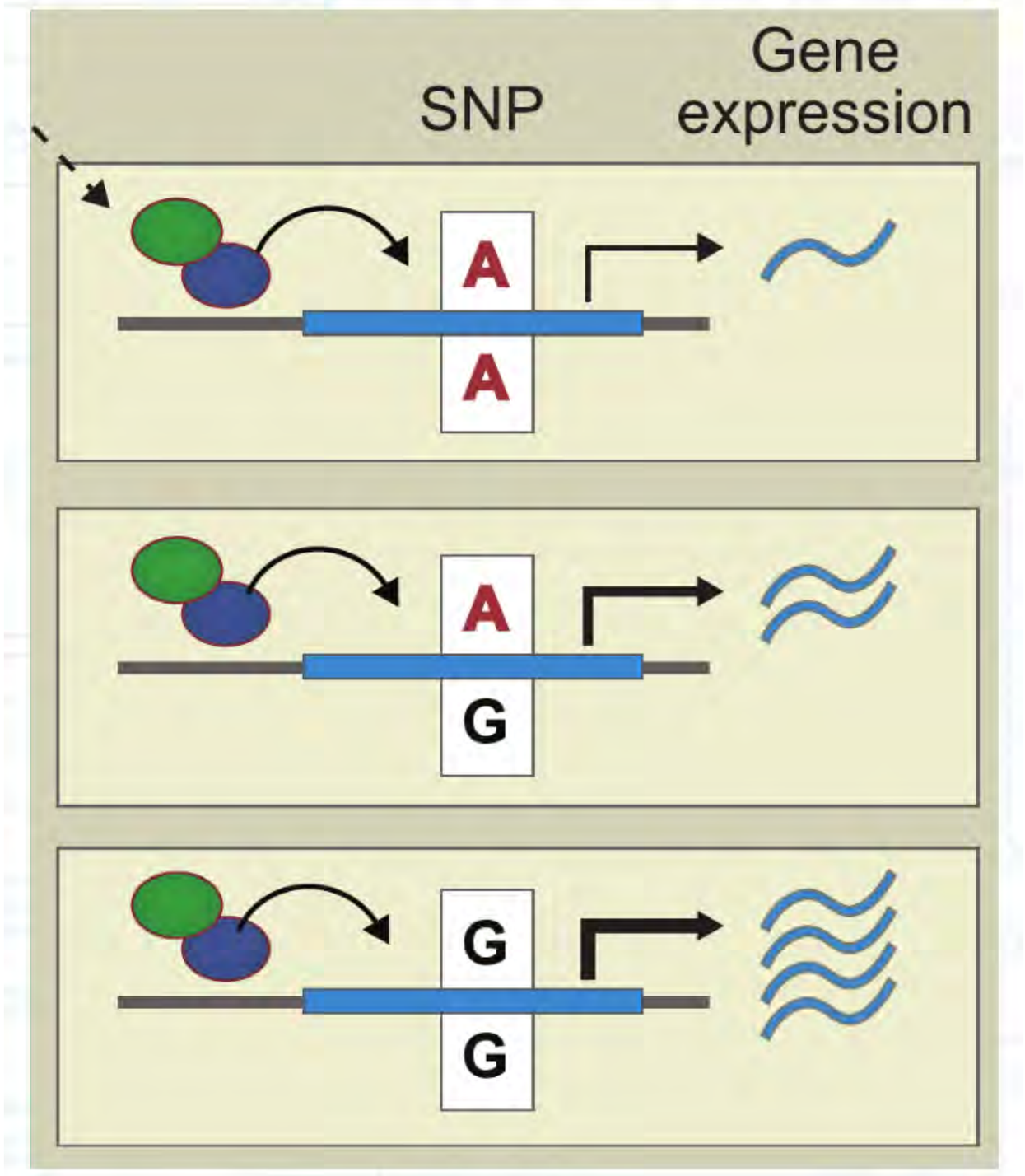
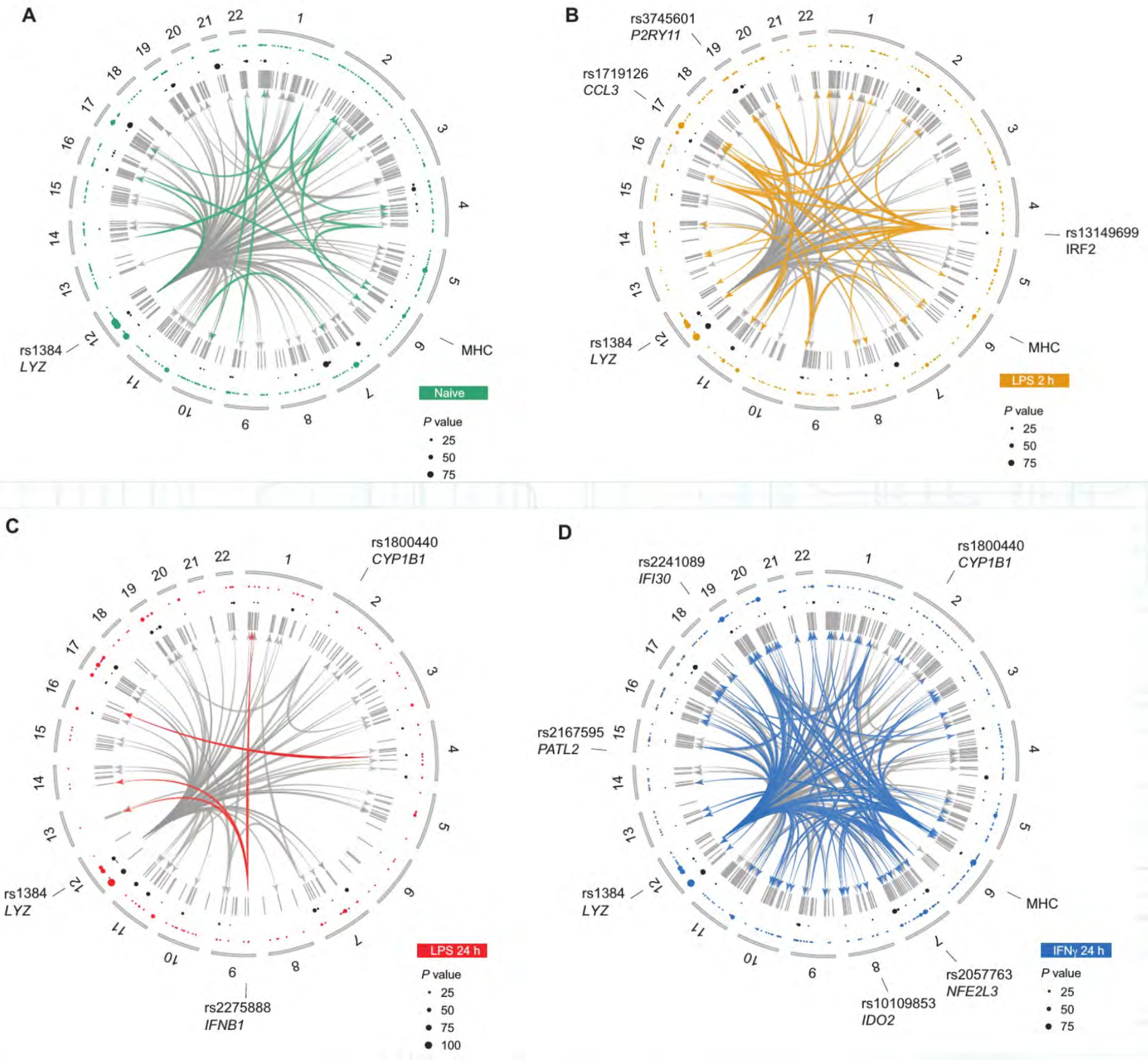
Web: dudleylab.org

precisionwellness.org

Icahn School of Medicine at
Mount Sinai

It's all about context

- eQTL
  - What?
  - Where?
  - When?



It's all about context