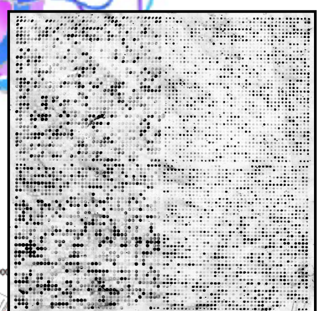
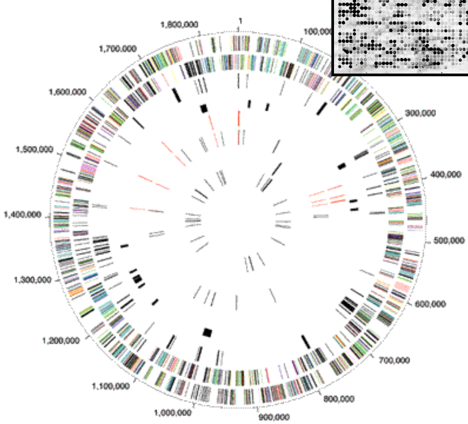
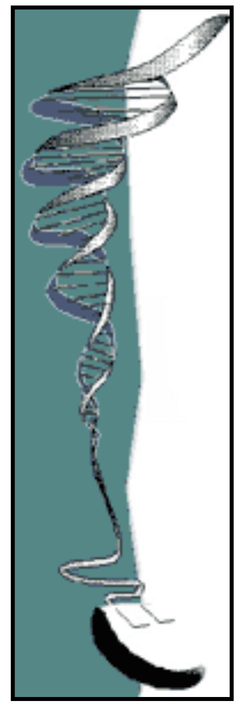
Biomedical Data Science: An Introduction







Mark Gerstein
Yale University

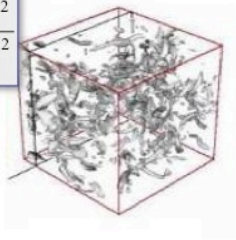
Overview: what is Biomed. Data science?

(Placing it into the context of Data Science, in general)

Science Paradigms

- Thousand years ago:
  science was **empirical**
  describing natural phenomena
- Last few hundred years:
  theoretical branch
  using models, generalizations
- Last few decades:
  a **computational** branch
  simulating complex phenomena
- Today:
  data exploration (eScience)
  unify theory, experiment, and simulation
  – Data captured by instruments
    Or generated by simulator
  – Processed by software
  – Information/Knowledge stored in computer
  – Scientist analyzes database / files
    using data management and statistics

$$\left(\frac{\dot{a}}{a}\right)^2 = \frac{4\pi G\rho}{3} - K\frac{c^2}{a^2}$$



#3 - Simulation

Prediction based on physical principles (eg Exact Determination of Rocket Trajectory)

Emphasis on: Supercomputers

#4 - Data Science

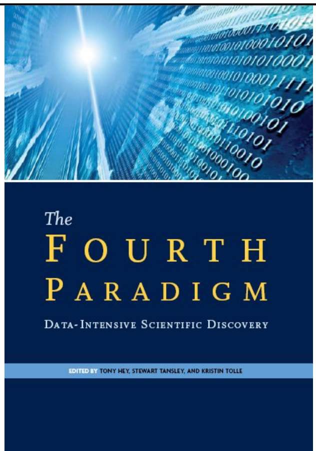
Data gathering and storing

Data analysis including data mining, modeling, visualizing

Creative use of data exhaust and protection of privacy

Emphasis: networks, “federated” DBs

Gray died in ’07.
Book about his ideas came out in ‘09…..



[Slide from : http://research.microsoft.com/en-us/um/people/gray/talks/stanford%2520symbolic%2520systems%2520seminar.ppt]

What is Data Science? An overall, bland definition…

- Data Science encompasses the study of the entire **lifecycle of data**
  - Understanding of how data are **gathered** & the issues that arise in its collection
  - Knowledge of what data sources are available & how they may be synthesized to solve problems
  - The **storage**, access, annotation, management, & transformation of data
- Data Science encompasses many aspects of **data analysis**
  - Statistical inference, machine learning, & the design of algorithms and computing systems that enable **data mining**
  - Connecting this mining where possible with **physical modeling**
  - The presentation and **visualization** of data analysis
  - The use of data analysis to make **practical decisions** & policy
- Secondary aspects of data, not its intended use – eg the **data exhaust**
  - The appropriate protection of **privacy**
  - Creative **secondary uses** of data – eg for Science of science
  - The elimination of inappropriate bias in the entire process

- Ads, media, product placement, supply optimization,
- Integral to success of GOOG, FB, AMZN, WMT…

Data Science in the wider world: a buzz-word for successful Ads

Forbes · New Posts +36 posts this hour · Most Popular 16-Year-Old Innovator · Lists Promising Companies

CIO Network
INSIGHTS AND IDEAS FOR TECHNOLOGY LEADERS.
+ Follow (469)

TECH | 12/12/2012 @ 1:57AM | 3,289 views

Why Big Data Is All Retailers Want for Christmas

Eric Savitz, Forbes Staff

+ Comment Now + Follow Comments

Guest post written by Quentin Gallivan

Quentin Gallivan is CEO of Pentaho Corp., an Orlando, Florida-based provider of business analytics software.

Harvard Business Review

Data Scientist: The Sexiest Job of the 21st Century

by Thomas H. Davenport and D.J. Patil

Artwork: **Tamar Cohen, *Andrew J Buboltz***, 2011, silk screen on a page from a high

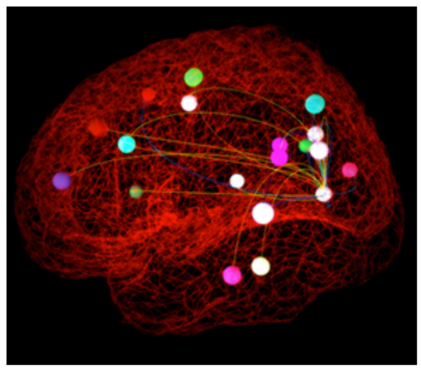
When Jonathan Goldman arrived for work in June 2006 at LinkedIn, the business ne up. The company had just under 8 million accounts, and the number was growing qu friends and colleagues to join. But users weren't seeking out connections with the pe

[Oct. '12 issue]

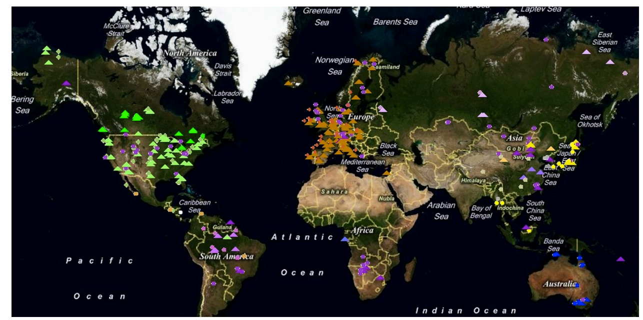
Data Science in Traditional Science

- Pre-dated commercial mining
- Instrument generated
- Large data sets often created by large teams not to answer one Q but to be mined broadly
- Often coupled to a physical/biological model
- Interplay w/ experiments

High energy physics - Large Hadron Collider

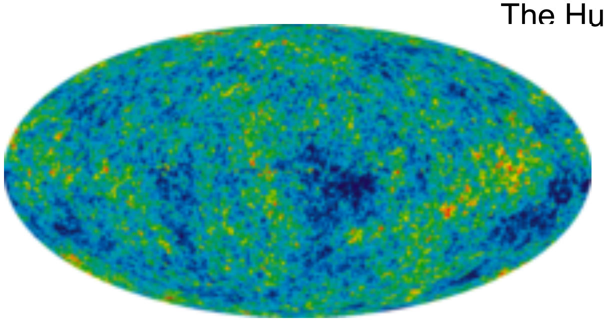


Neuroscience - The Human Connectome Project



Ecology & Earth Sci. - Fluxnet

Genomics DNA sequencer



Astronomy - Sloan Digital Sky survey

Coupling of Scientific Data to Models & Experiments

- Scientific data often coupled to a physical/biological model
- Lauffenburger's Sys. Biol. **4Ms:**
  Measurement, Mining, Modeling & Manipulation
  (Ideker et al.'06. Annals of Biomed. Eng.)
- Weather forecasting as an exemplar
  - Physical models & simulation useful but not sufficient ("butterfly" effect)
  - Success via coupling to large-scale sensor data collection

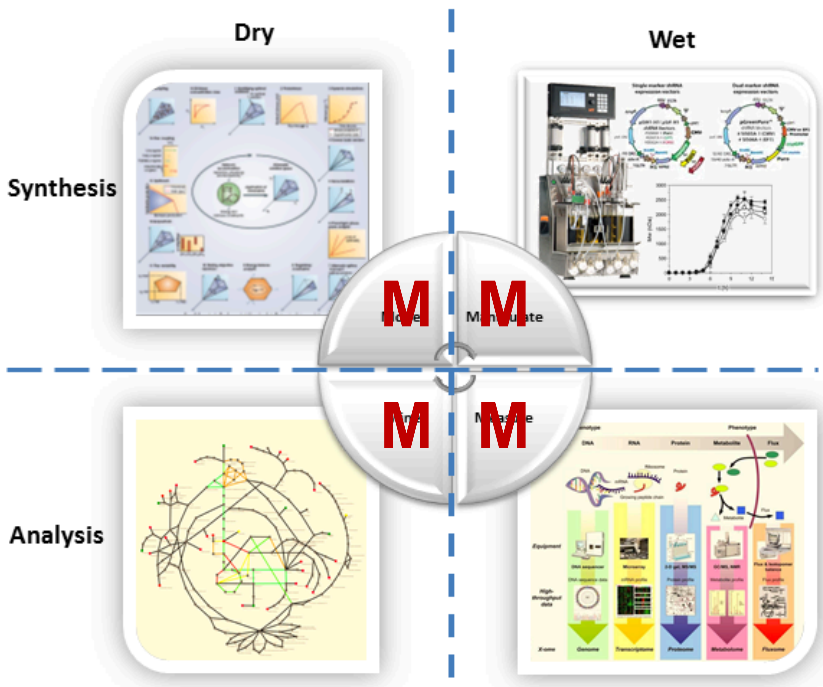
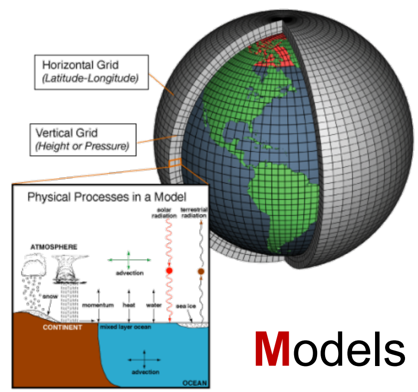
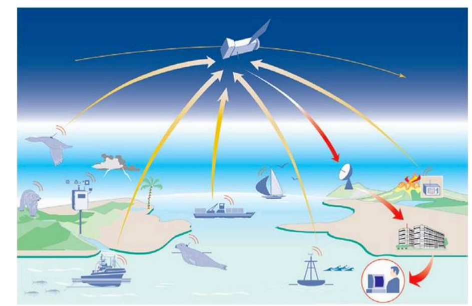


Image from http://web.aibn.uq.edu.au/cssb/ResearchProjects.htm

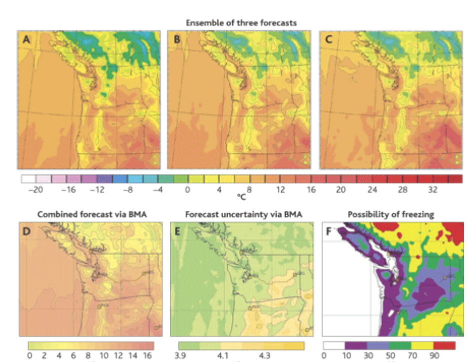




Models + Data Mining

↓

Forecasts



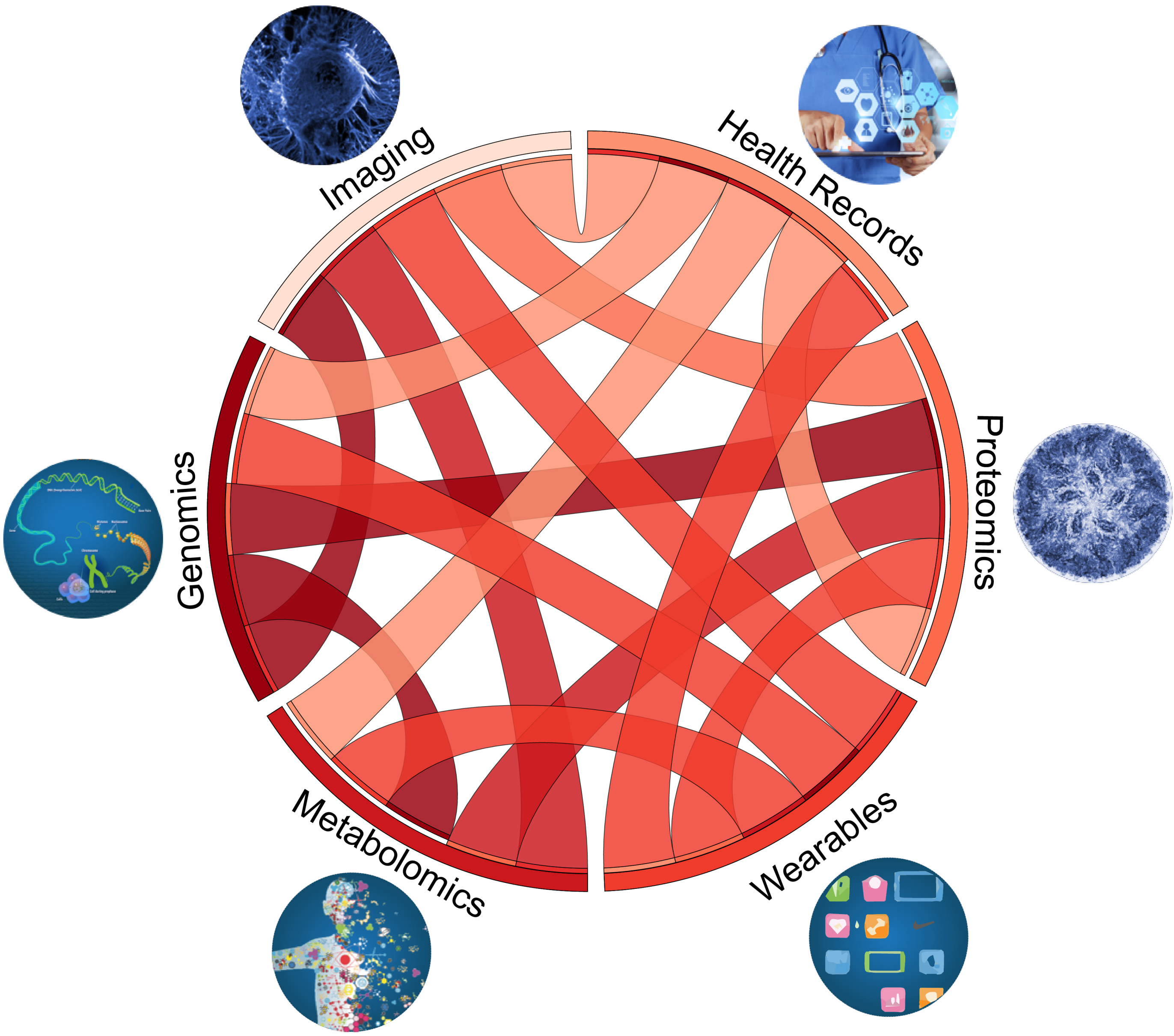
NOAA

Biomed. Data science:

Scaling & Integration

Drivers of Biomedical Data Science

- **Integration** across data types
- **Scaling** of individual data types



Case Study: Amazing Progress in Scaling & Integration with Genotype-Phenotype Relationships

1953

Double Helix

Watson & Crick

1995

Sequenced Genome

H. influenzae

2008

1000 Genomes

Catalogue of human variation

2015

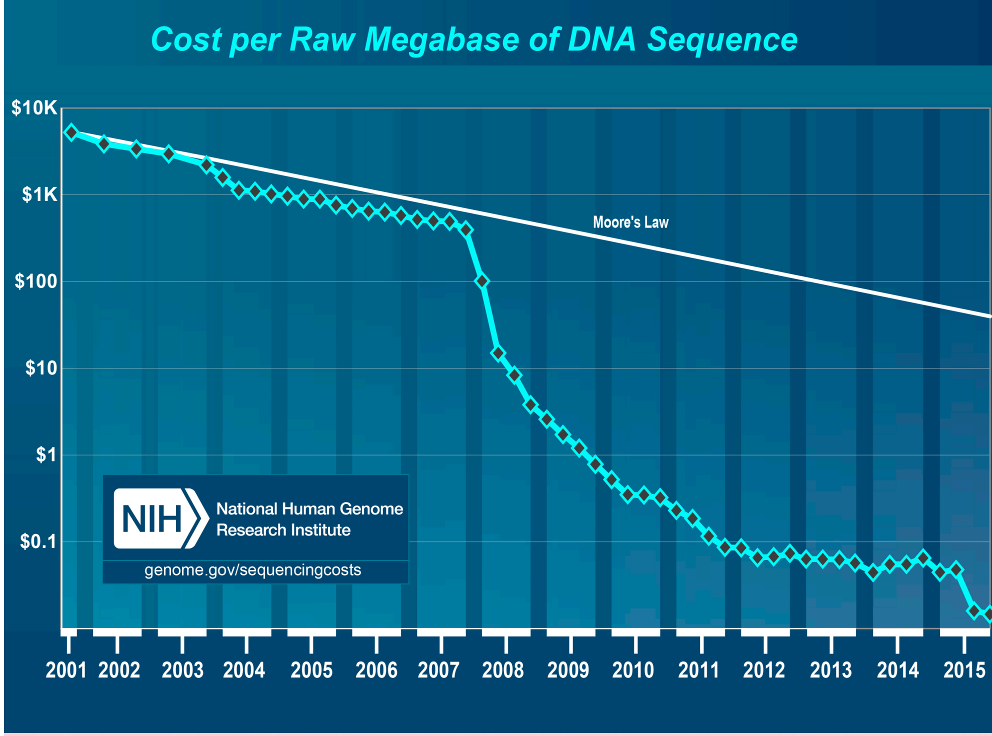
Integrated health data

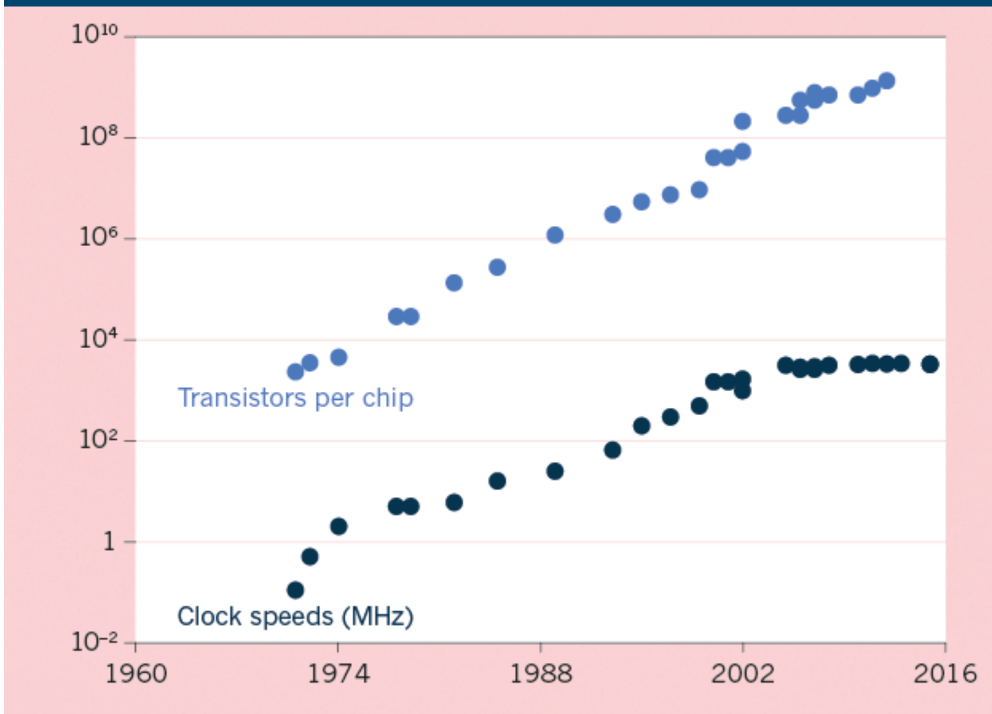
UKBB study with over 500K participants, genotypes to phenotypic details & clinical information

The Scaling of Genomic Data Science:

Powered by exponential increases in data & computing

(Moore's Law)

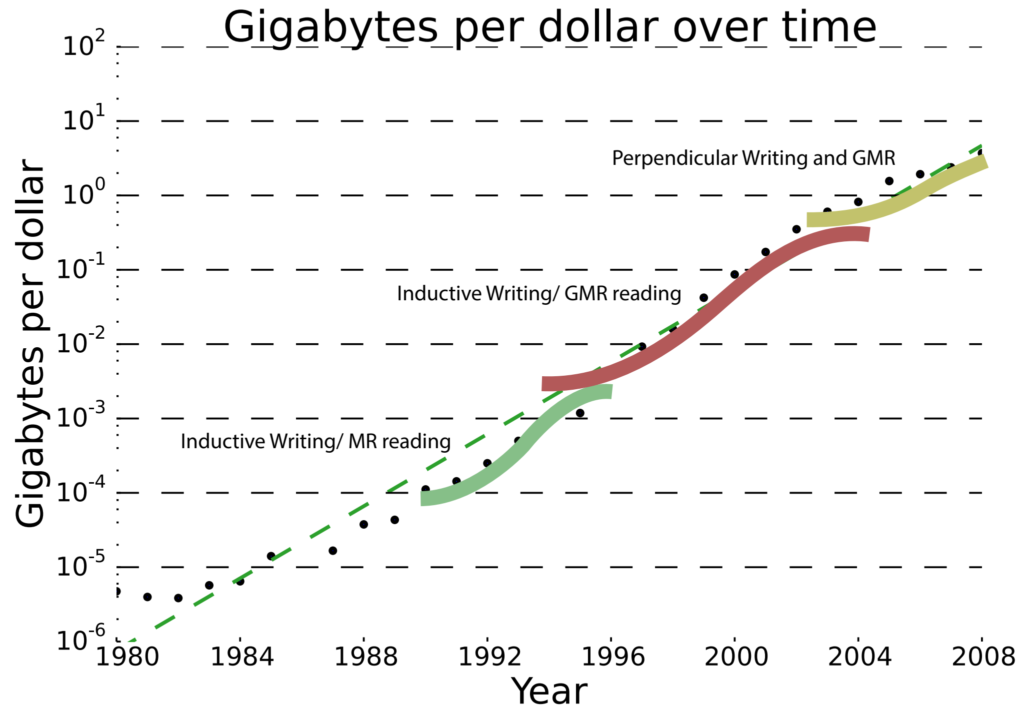


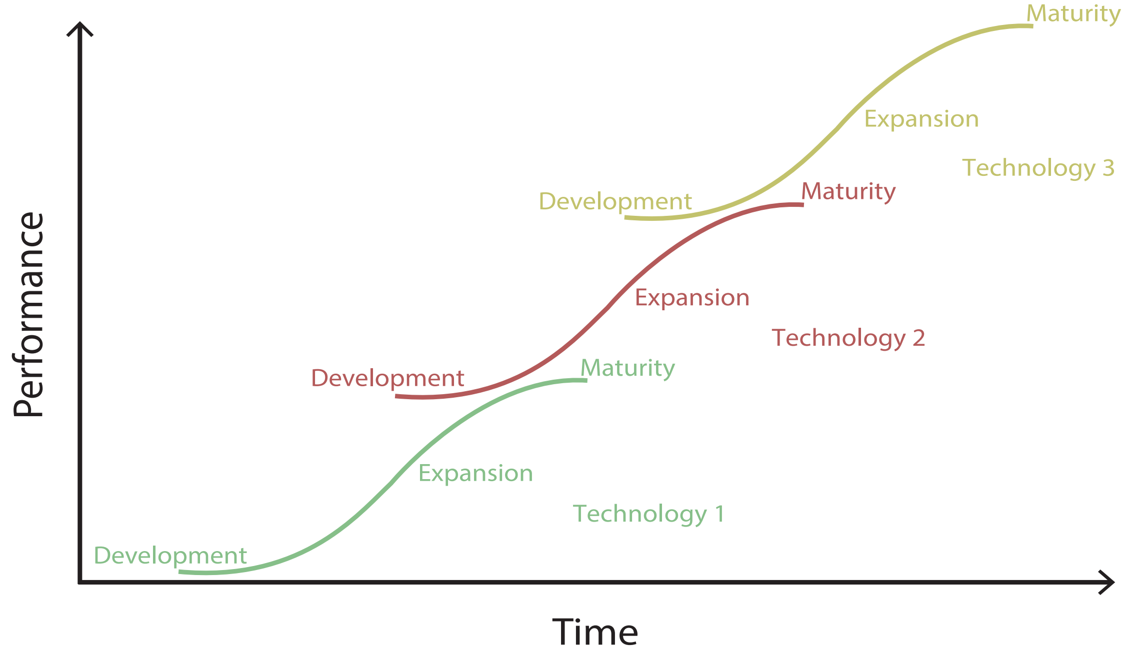


[NHGRI website + Waldrop ('15) Nature]

Kryder's Law and S-curves underlying exponential growth

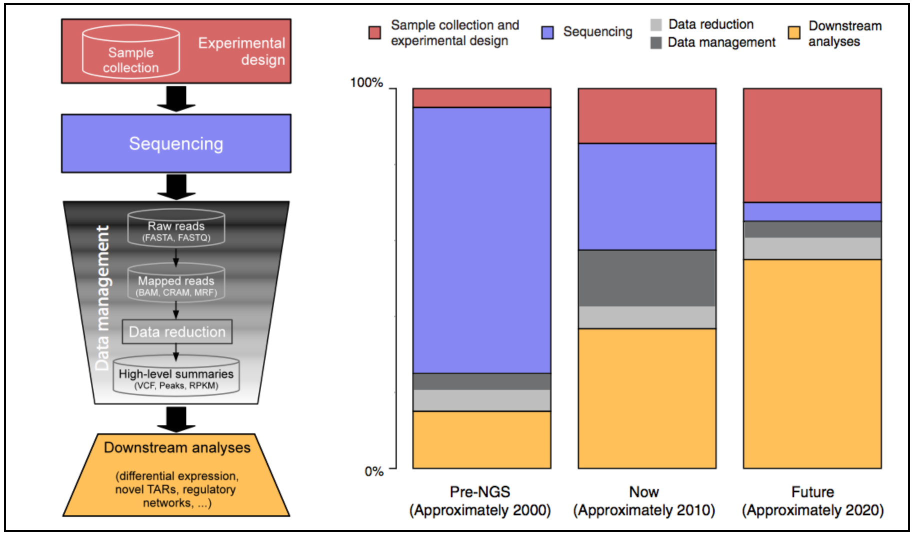
- Exponential increase seen in Kryder's law is a superposition of S-curves for different technologies





[Muir et al. ('15) GenomeBiol.]

The changing costs of a sequencing pipeline



From ‘00 to ~’ 20,
cost of DNA sequencing expt. shifts from the actual seq. to sample collection & analysis

[Sboner et al. (‘11), Muir et al. (‘15) Genome Biology]

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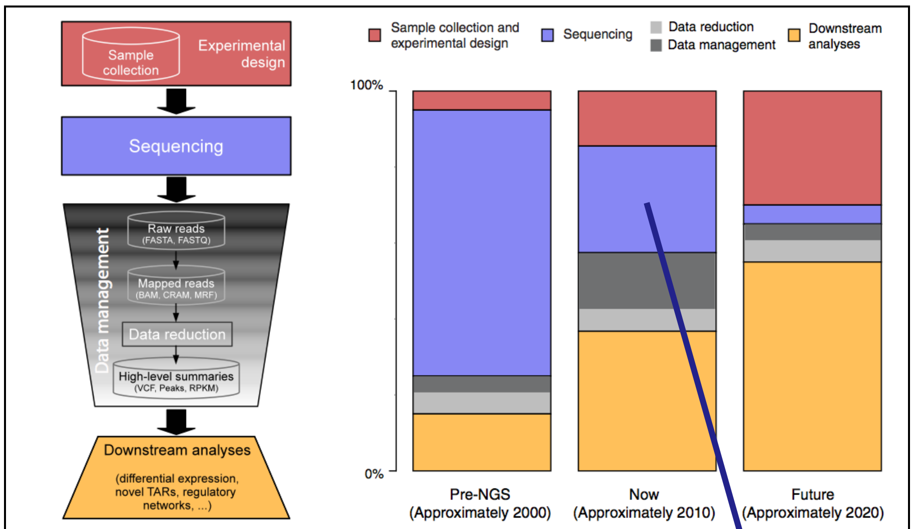

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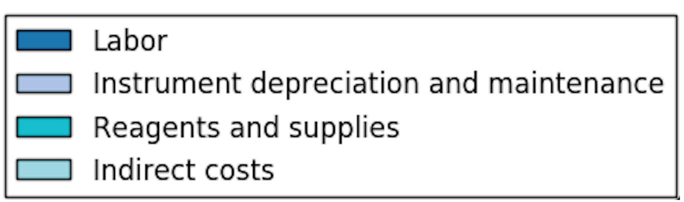
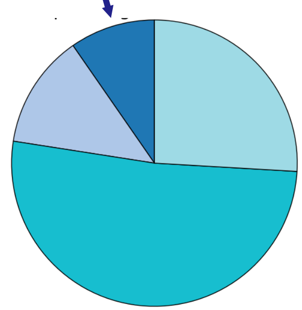
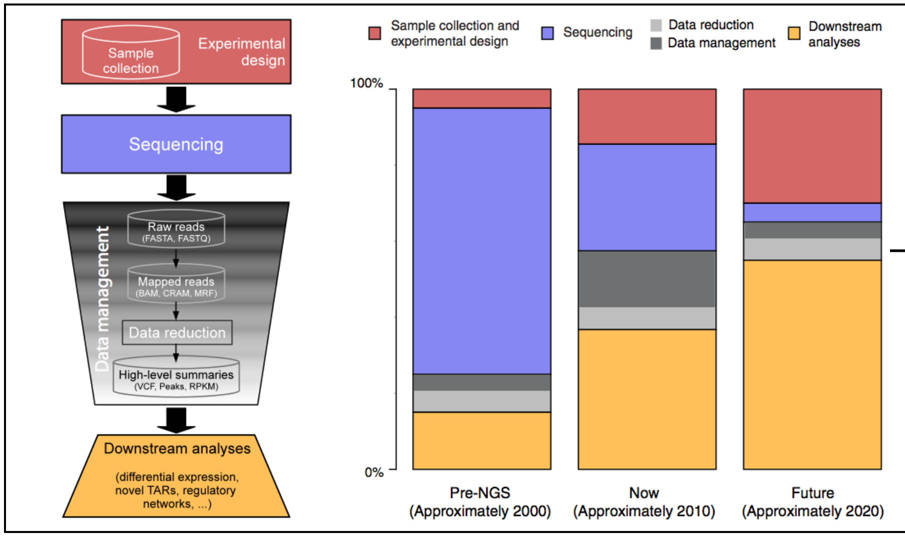
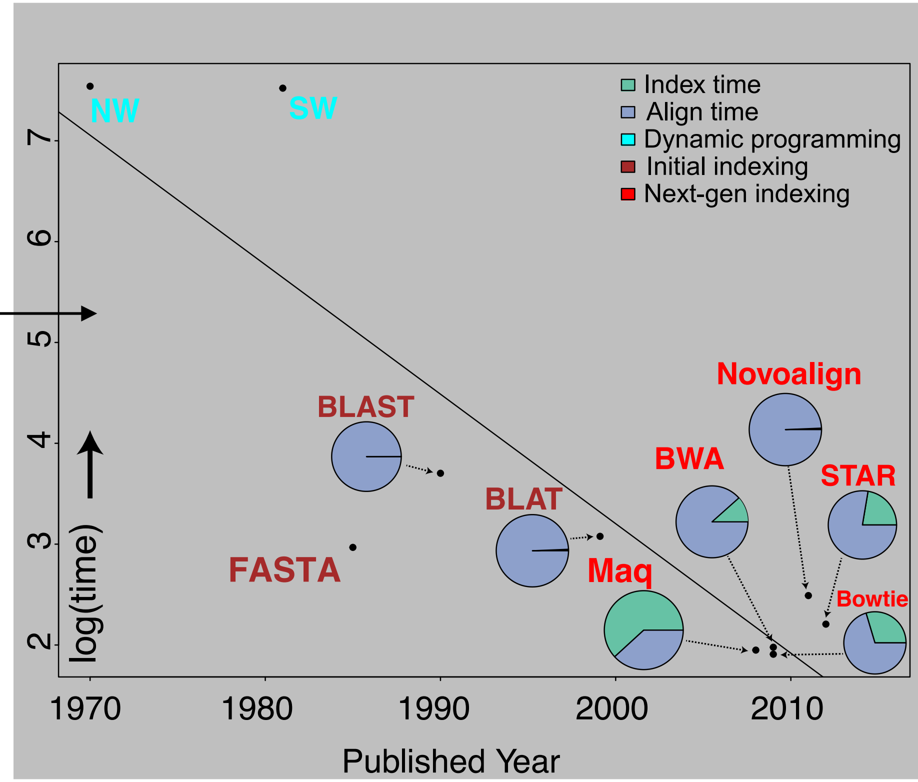




[Sboner et al. (‘11), Muir et al. (‘15) Genome Biology]

The changing costs of a sequencing pipeline



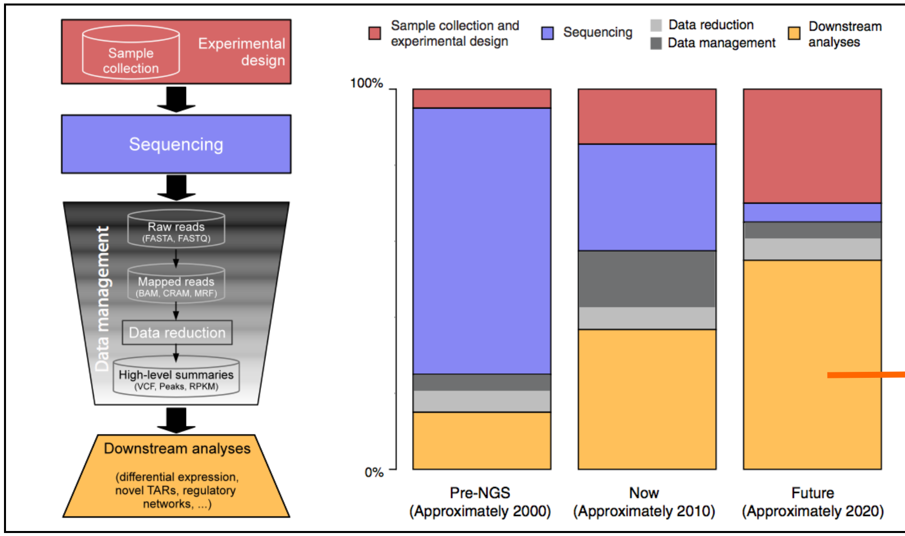


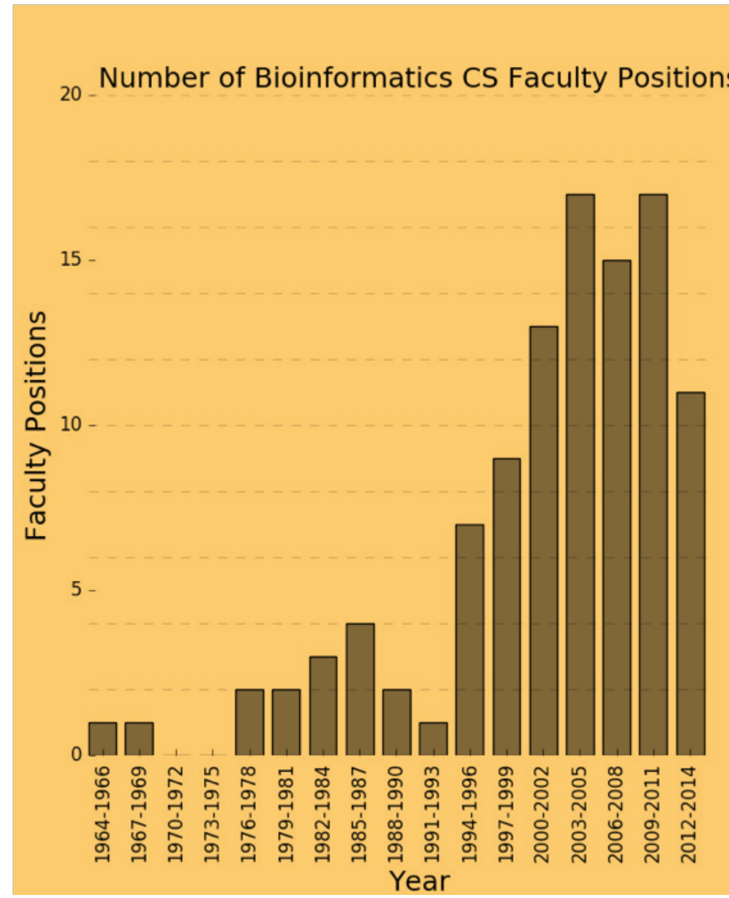
From '00 to ~'20,
cost of DNA sequencing expt. shifts from the actual seq. to sample collection & analysis

Alignment algorithms scaling to keep pace with data generation

[Sboner et al. ('11), Muir et al. ('15) Genome Biology]

The changing costs of a sequencing pipeline

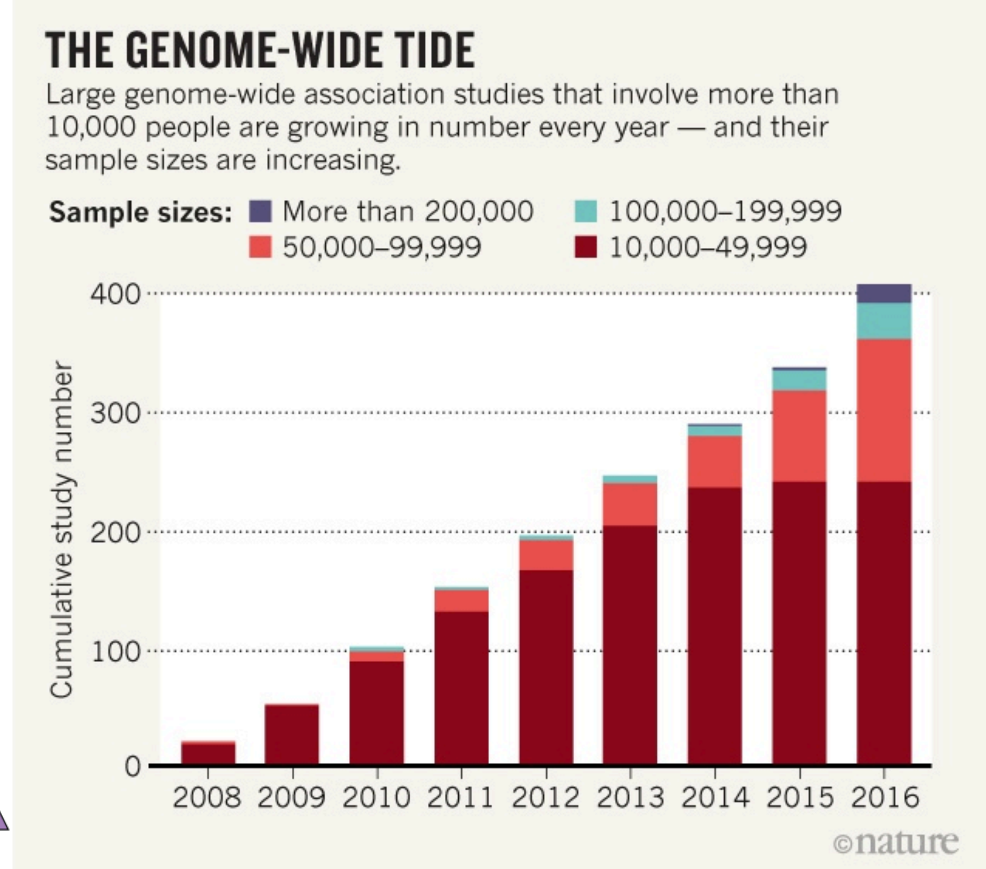


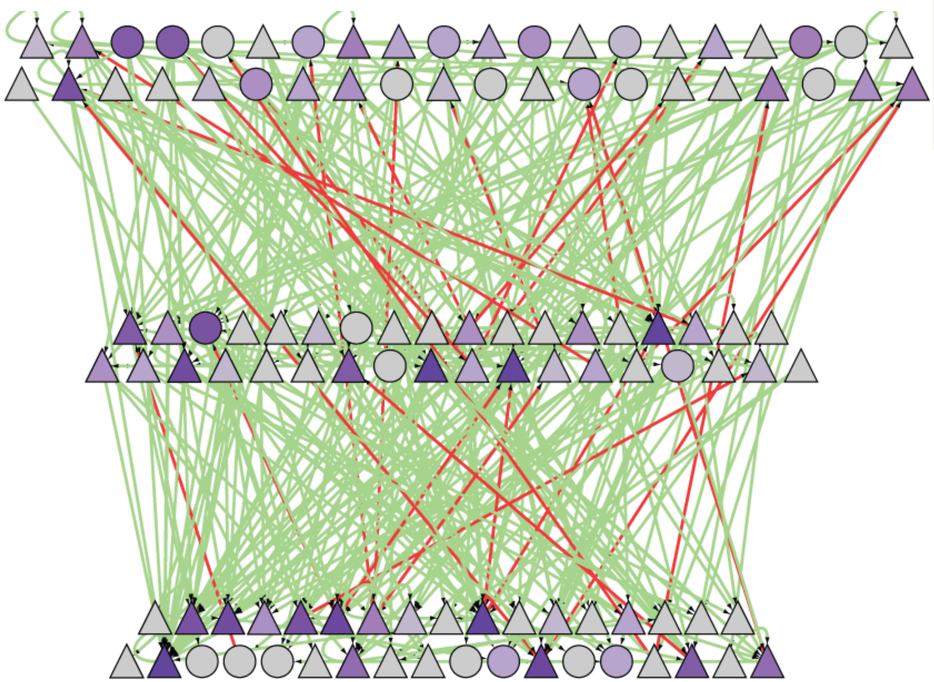


From ‘00 to ~’ 20,
cost of DNA sequencing expt. shifts from the actual seq. to sample collection & analysis

[Sboner et al. (‘11), Muir et al. (‘15) Genome Biology]

A Success of Scale & Integration: Many GWAS variants found, most not in genes, but affecting regulatory network





- A 1st GWAS done at Yale, for AMD: (Klein et al. 05, Science)
- Many since then
- Most SNVs fall into non-coding regulatory regions
  (major contributions by Yale groups to this ENCODE annotation effort)

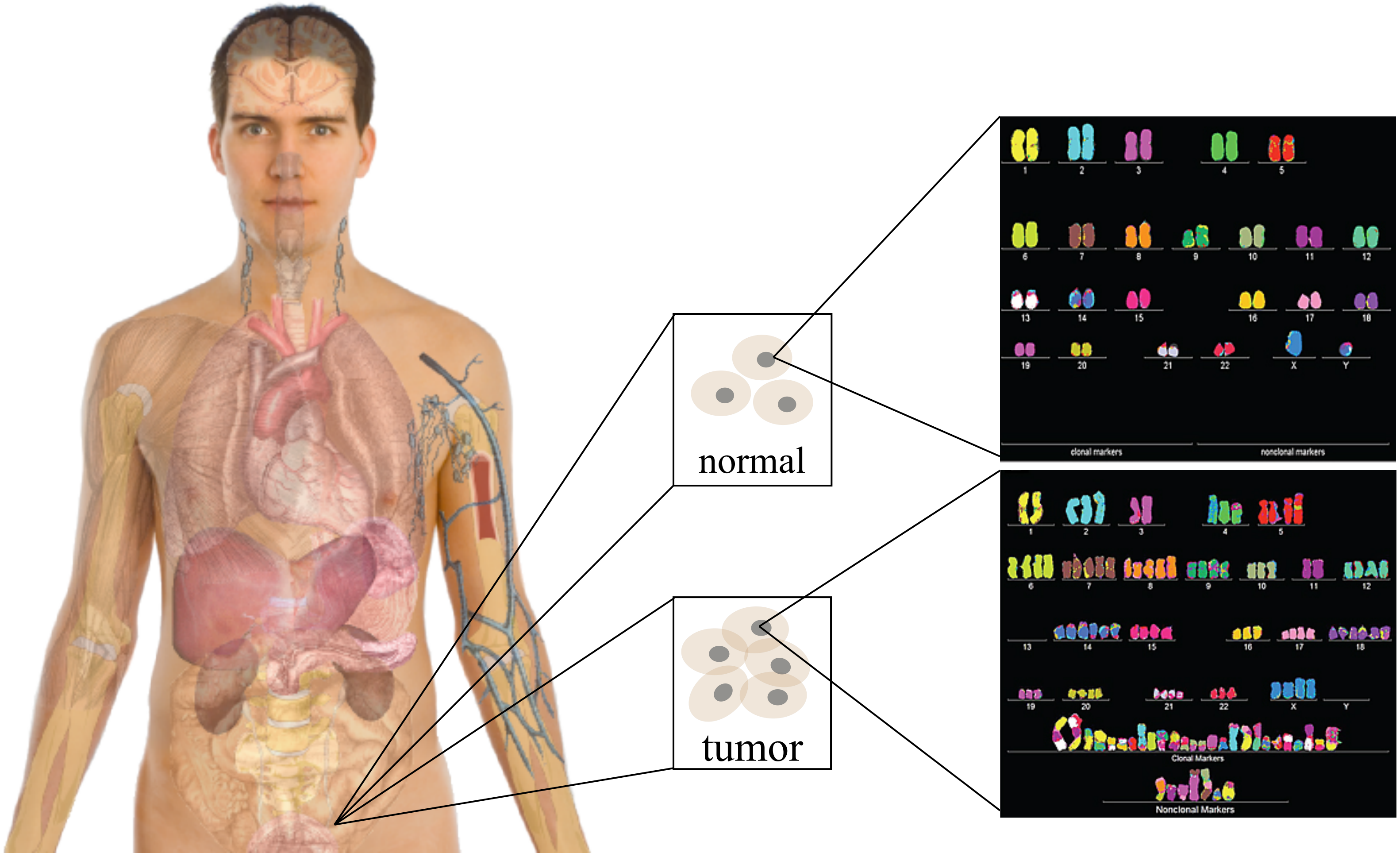
[*Nature* 489: 91]

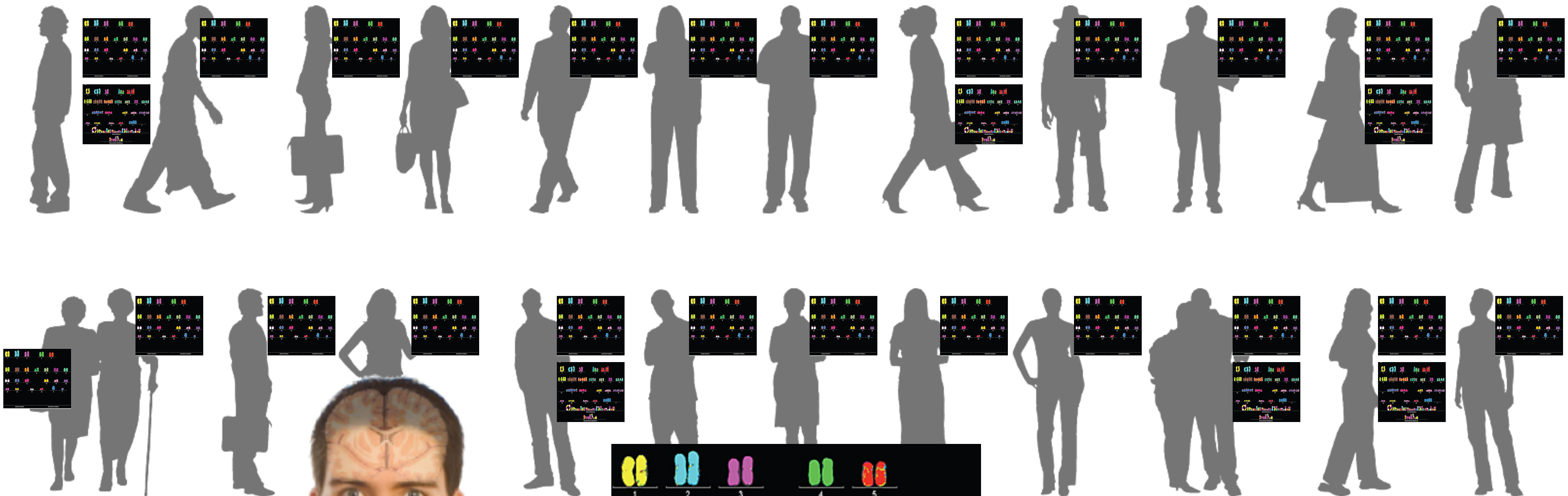
Biomed. Data science:

The Future

Our field as future Gateway – Personal Genomics as a Gateway into Biology

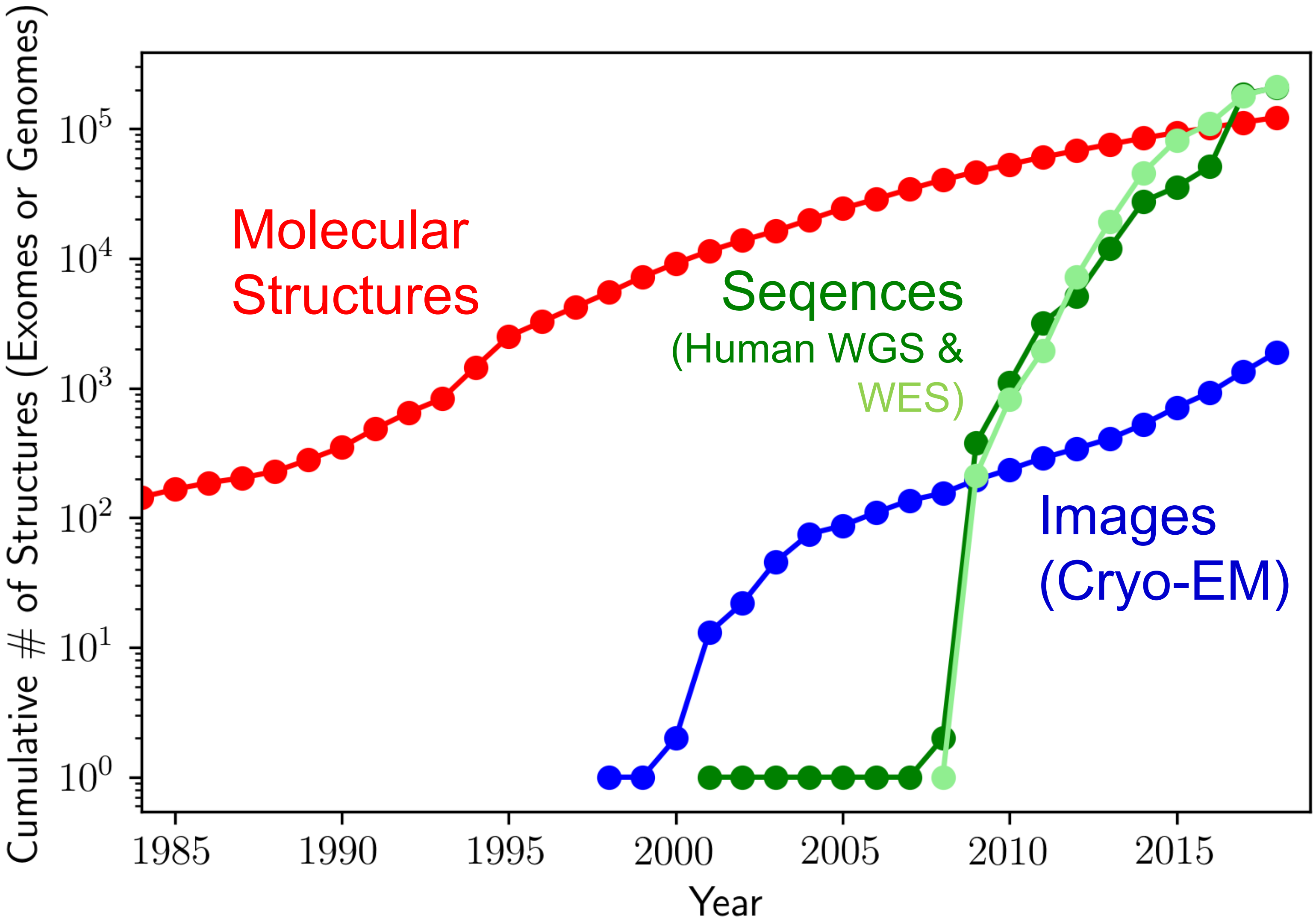
Personal genomes soon will become a commonplace part of medical research & eventually treatment (esp. for cancer). They will provide a primary connection for biological science to the general public.





Placing the individual into the context of the population
&
using the population to build a interpretative model

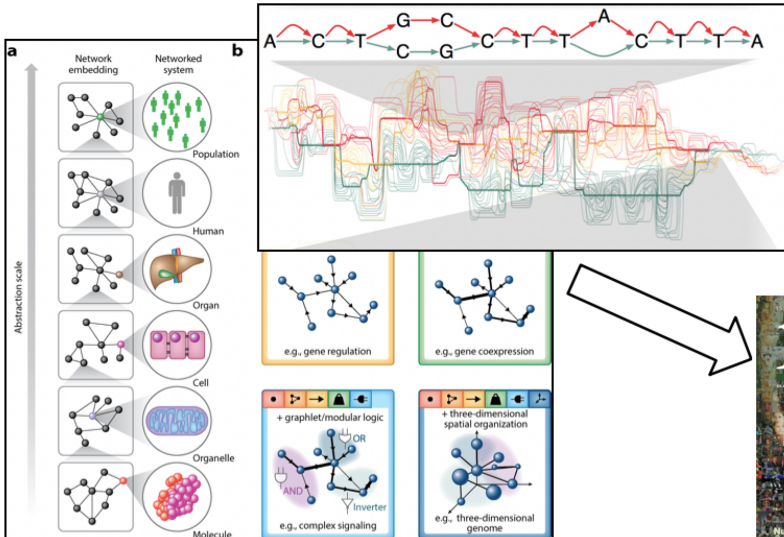
How will the Data Scaling Continue? The Past, Present & Future Ecosystem of Large-scale Biomolecular Data



Examples of Imports & Exports to/from Genomics & Other Data Science Application Areas

Technical Imports

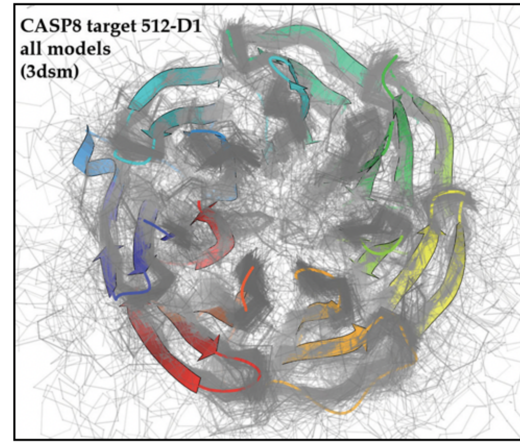
Networks and graphs



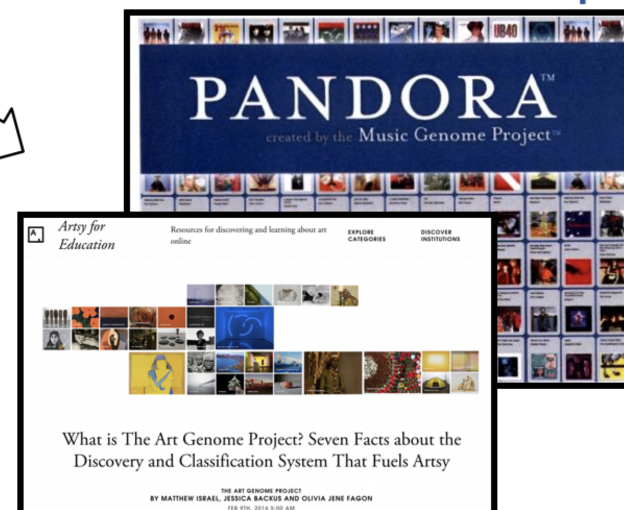
Importing tech. developed in other big data disciplines

Cultural Imports

CASP

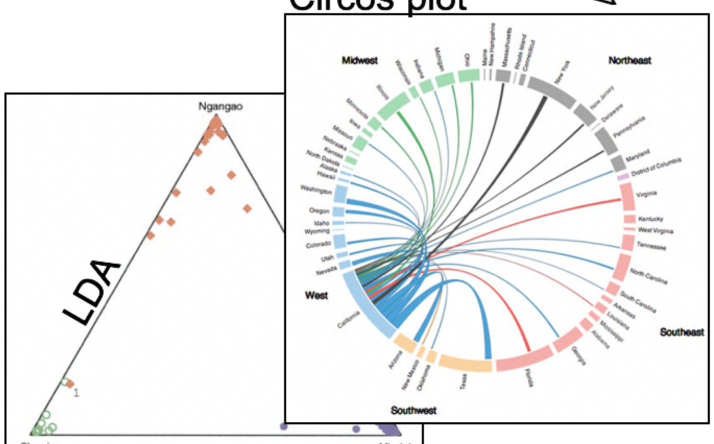


Cultural Exports

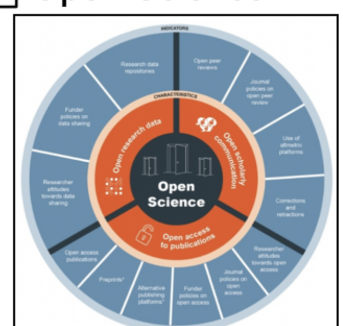


Technical Exports

Circos plot



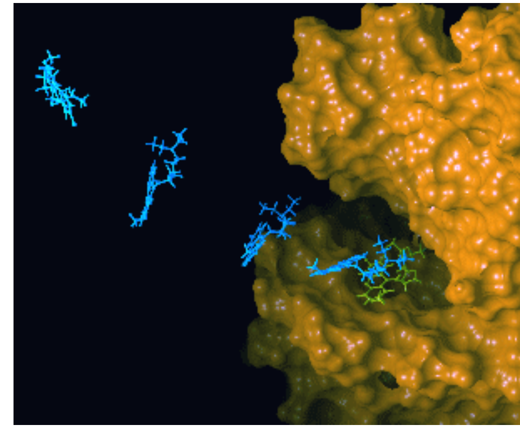
Open Science



Bioinformatics

Key Practical Applications

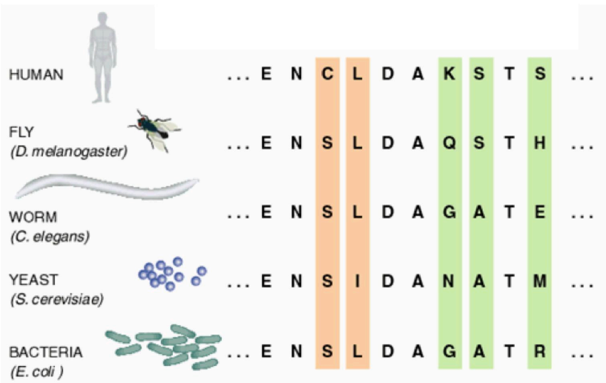
Major Bioinformatics Applications



Adapted from Olsen Group Docking Page at Scripps

I. Designing Drugs from Structural Targets

- Understanding how structures bind other molecules
- Designing inhibitors using docking, structure modeling

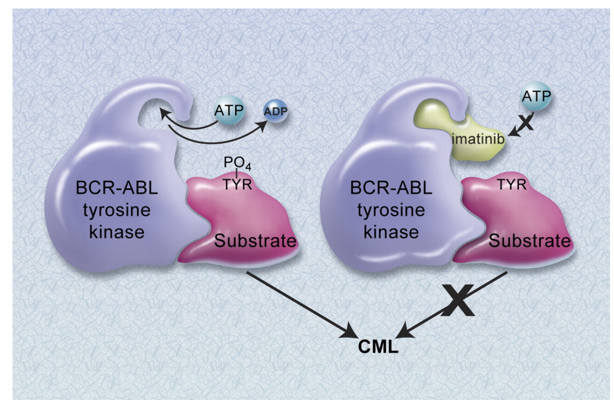


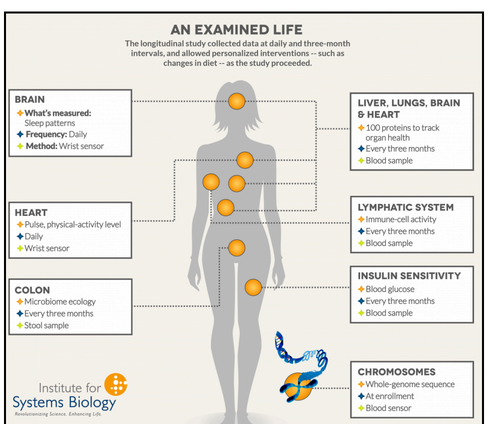
II. Finding Homologs

- Model structures based on currently available structures
- Find experimentally tractable gene targets

III. Customizing treatment in oncology

- Identifying key disease causing mutations
- Cancer immunotherapies targeting neo-antigens





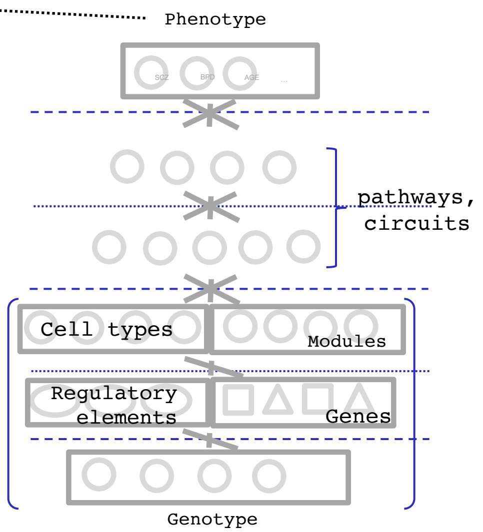
IV. Personal Genome Characterization

- Identify mutations in personal genomes (SNPs, SVs, &c)
- Integrate with digital phenotyping (eg wearables)

(From top to bottom: figures adapted from Olsen Group Docking Page at Scripps, Sci. Am., Druker BJ. Blood 2008, Institute for Systems Biology)

Major Application V:
Finding molecular mechanisms & drug targets
for diseases we know little about (Neuro-psychiatic Diseases)

Disease	Heritability*	Molecular **Mechanisms**
Schizophrenia	**81%**	**C4A**
Bipolar disorder	70%	**-**
Alzheimer's disease	58 - 79%	Apolipoprotein E (APOE), Tau
Hypertension	30%	Renin–angiotensin–aldosterone
Heart disease	34-53%	Atherosclerosis, VCAM-1
Stroke	32%	Reactive oxygen species (ROS), Ischemia
Type-2 diabetes	26%	Insulin resistance
Breast Cancer	25-56%	BRCA, PTEN



*https://www.snpedia.com/index.php/Heritability

Many psychiatric conditions are highly heritable
- Schizophrenia: up to 80%

But we don't understand basic molecular mechanisms underpinning this association
- (in contrast to many other diseases such as cancer & heart disease)

Thus, interested in developing predictive models of psychiatric traits which:
- Use observations at intermediate (molecular levels) levels to inform latent structure.
- Use the predictive features of these "molecular endo phenotypes" to begin to suggest actors involved in mechanism

Major Application V:
Finding molecular mechanisms & drug targets for diseases we know little about (Neuro-psychiatic Diseases)

Disease	Heritability*	Molecular **Mechanisms**
Schizophrenia	**81%**	**Complement Component 4A (C4A)**
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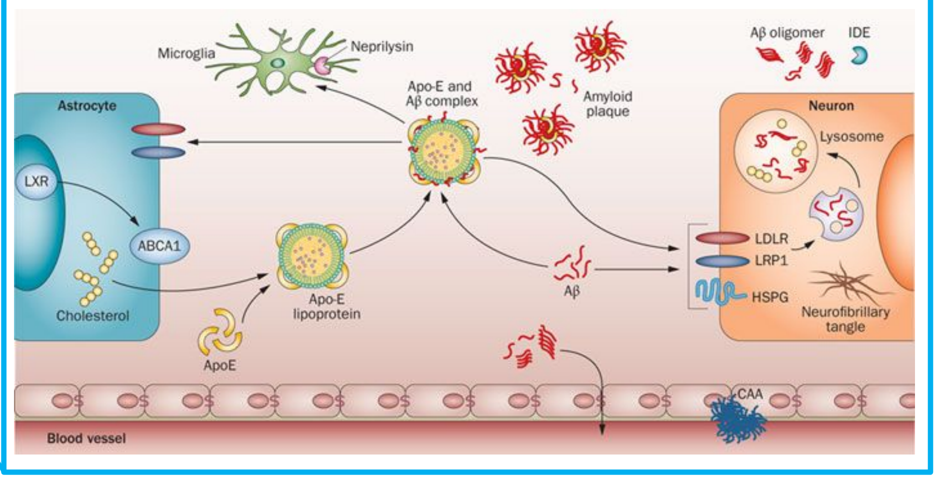

Image: www.nature.com/articles/nrneurol.2012.263

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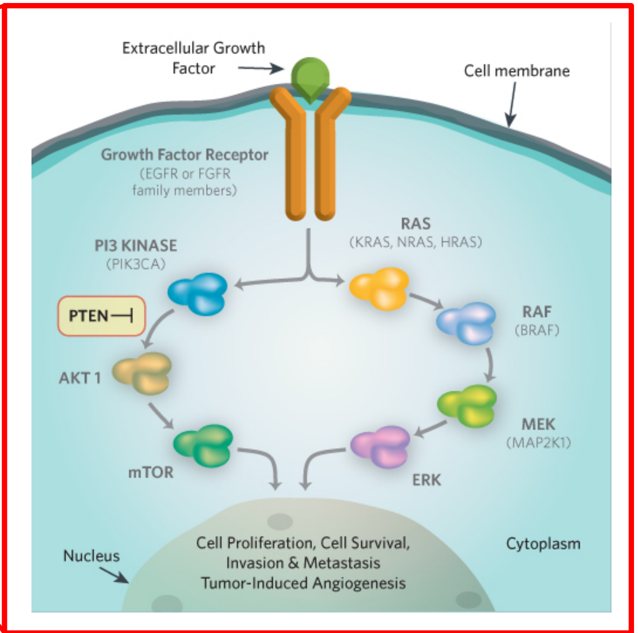

Image: targetedcancercare.massgeneral.org/My-Trial-Guide/Diseases/Lung-Cancer/PTEN.aspx

Major Application IV:
Finding molecular mechanisms & drug targets
for diseases we know little about (Neuro-psychiatic Diseases)

Disease	Heritability*	Molecular **Mechanisms**
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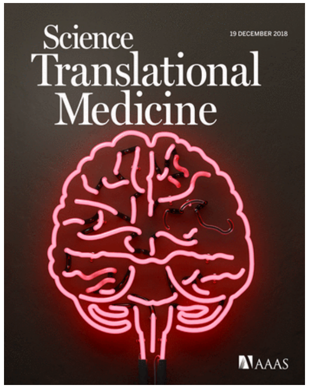
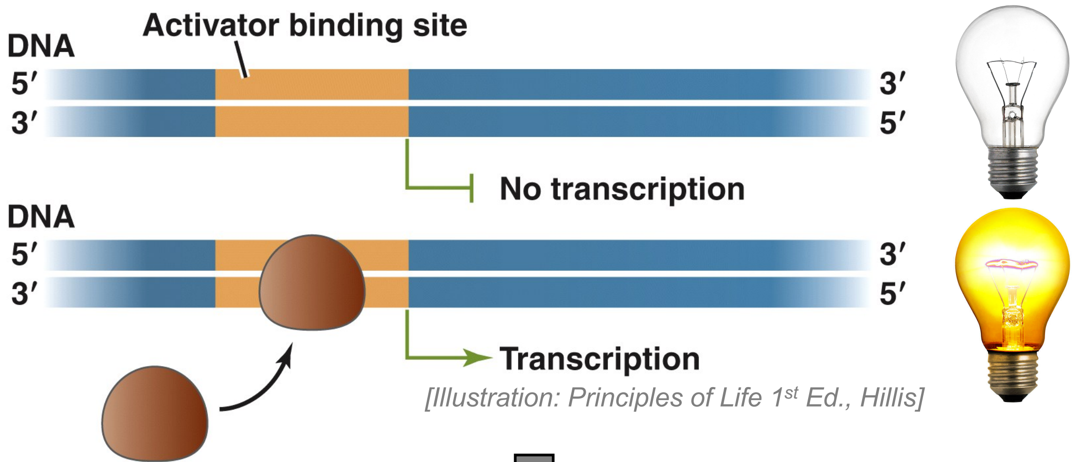
- Use the predictive ... to begin to suggest actors inv...

Recent Rollout in Science addressing this, involving many Yale Researchers



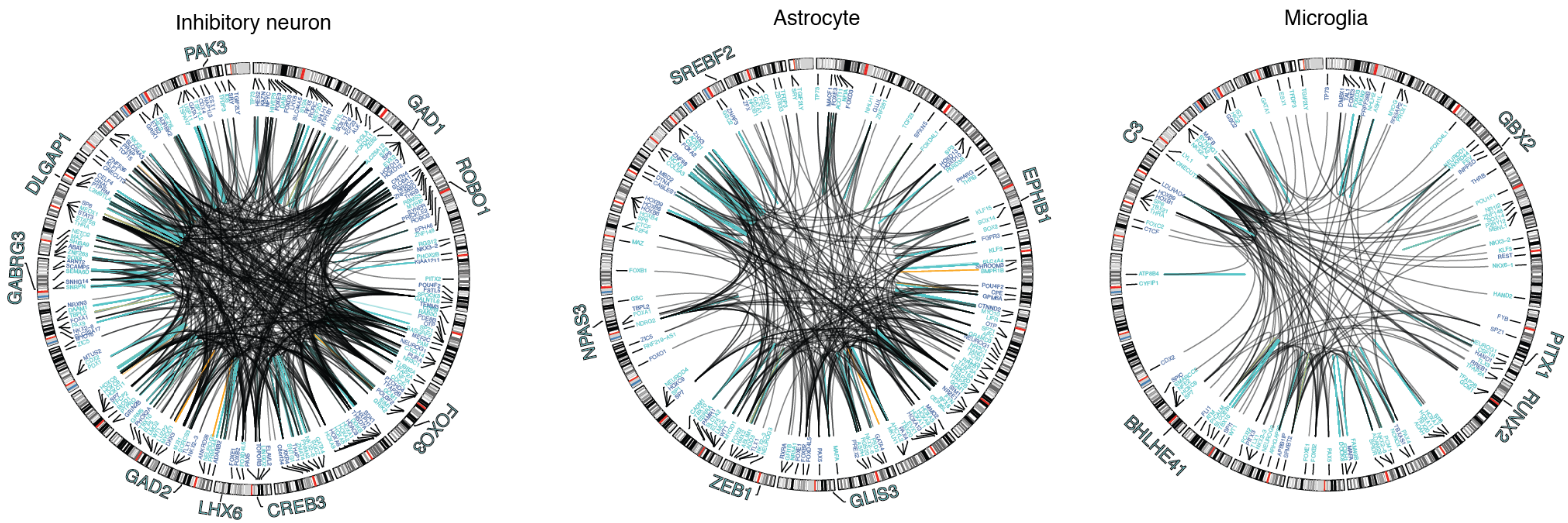
*https://www.snpedia.com/index.php/Heritability

Developing a gene regulatory network for the human brain



[Illustration: Principles of Life 1st Ed., Hillis]

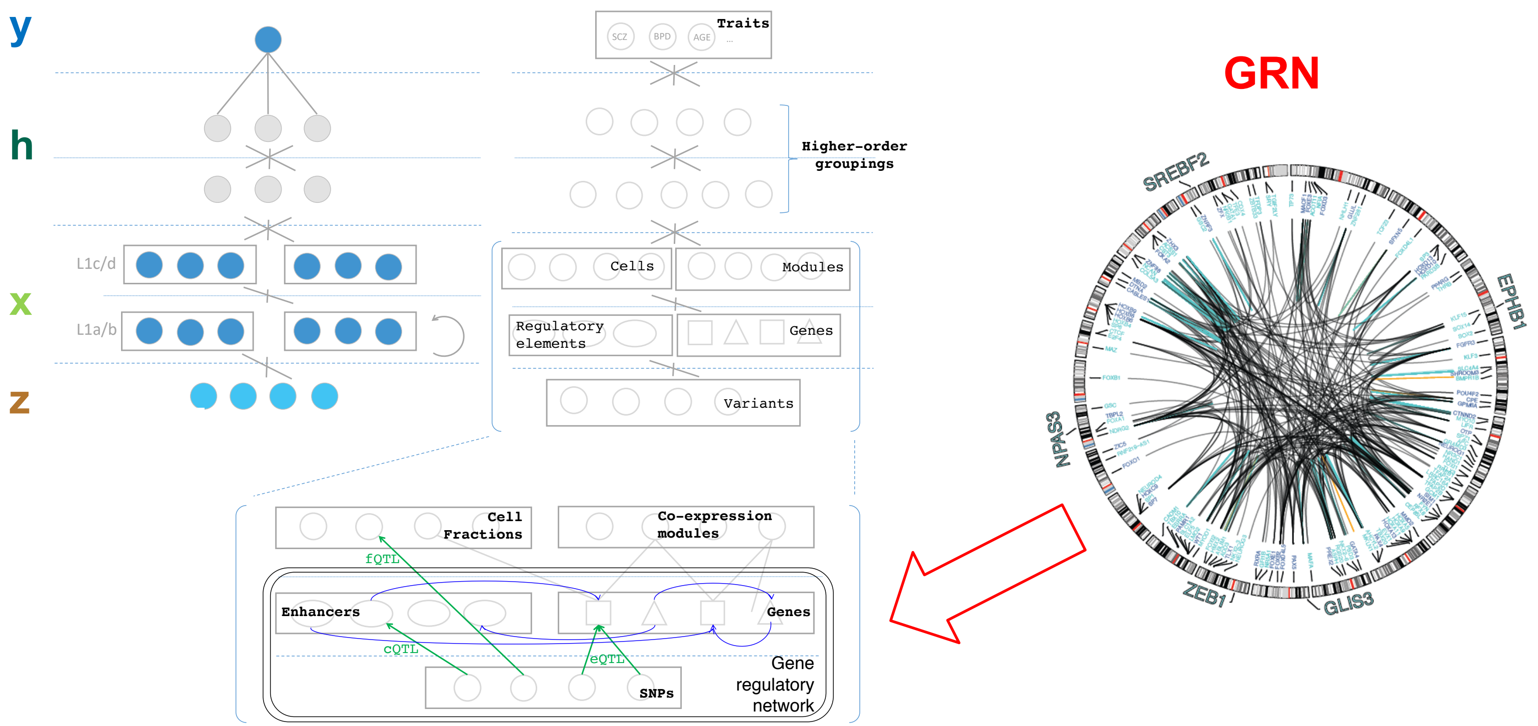
Many such gene regulatory relationships form a network



[Wang et al. ('18) Science]

Deep Structured Phenotype Network (DSPN)

- Embed **Gene Regulatory Network** in deep neural network
- Allows transcriptome (+other) imputation & trait prediction



y: phenotypes

h: hidden units (e.g., circuits)

x: intermediate phenotypes (e.g. expression, enhancers)

z: genotypes (e.g., SNPs)

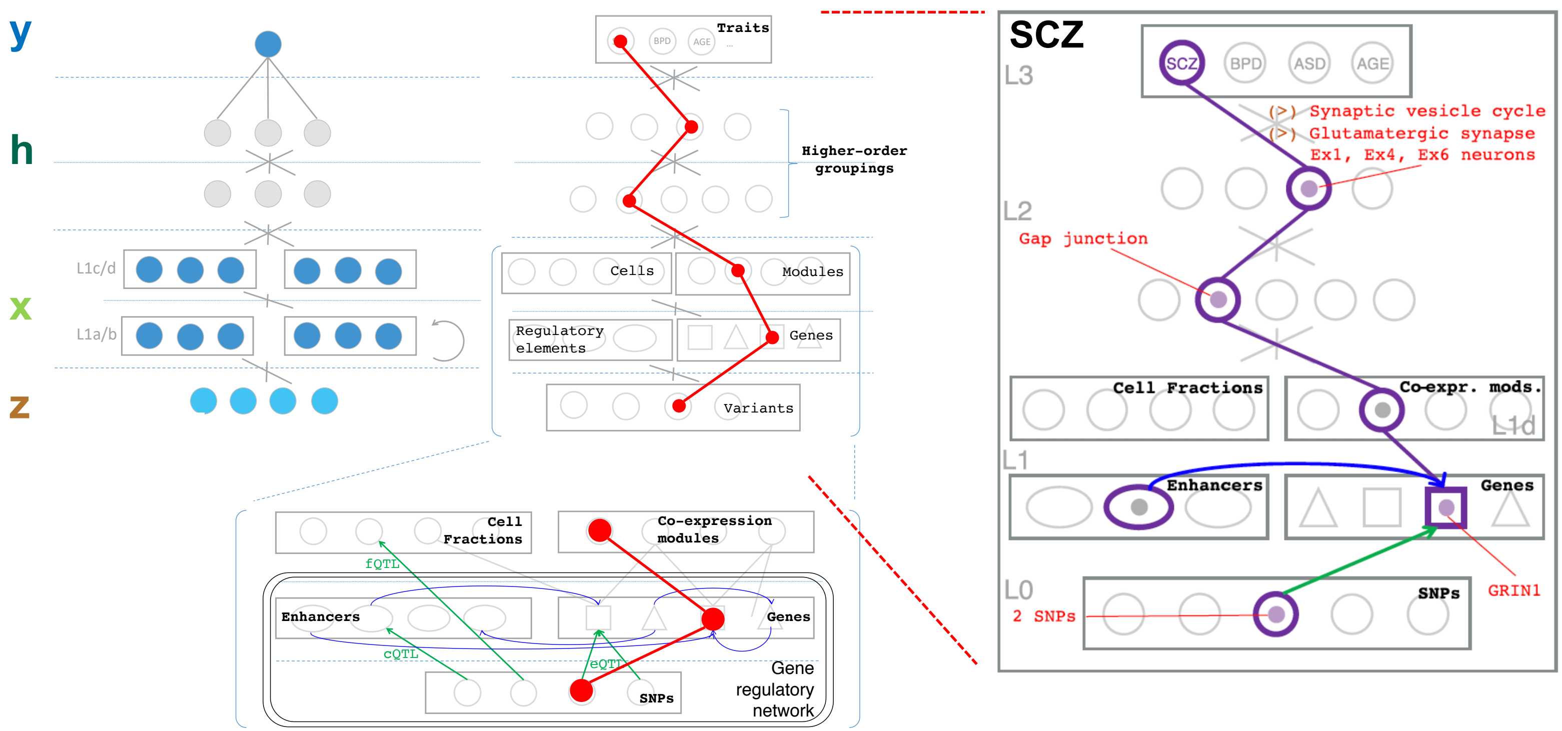
Deep Boltzmann Machine Energy model:

$$p(\mathbf{x},\mathbf{y},\mathbf{h}|\mathbf{z}) \propto \exp\big(-E(\mathbf{x},\mathbf{y},\mathbf{h}|\mathbf{z})\big)$$

[Wang et al. ('18) Science]

Deep Structured Phenotype Network (DSPN)

- **Allows prioritization of genes / modules through network interpretation (using path tracing)**



y: phenotypes

h: hidden units (e.g., circuits)

x: intermediate phenotypes (e.g. expression, enhancers)

z: genotypes (e.g., SNPs)

Deep Boltzmann Machine Energy model:

$$p(\mathbf{x},\mathbf{y},\mathbf{h}|\mathbf{z}) \propto \exp\big(-E(\mathbf{x},\mathbf{y},\mathbf{h}|\mathbf{z})\big)$$

[Wang et al. ('18) Science]

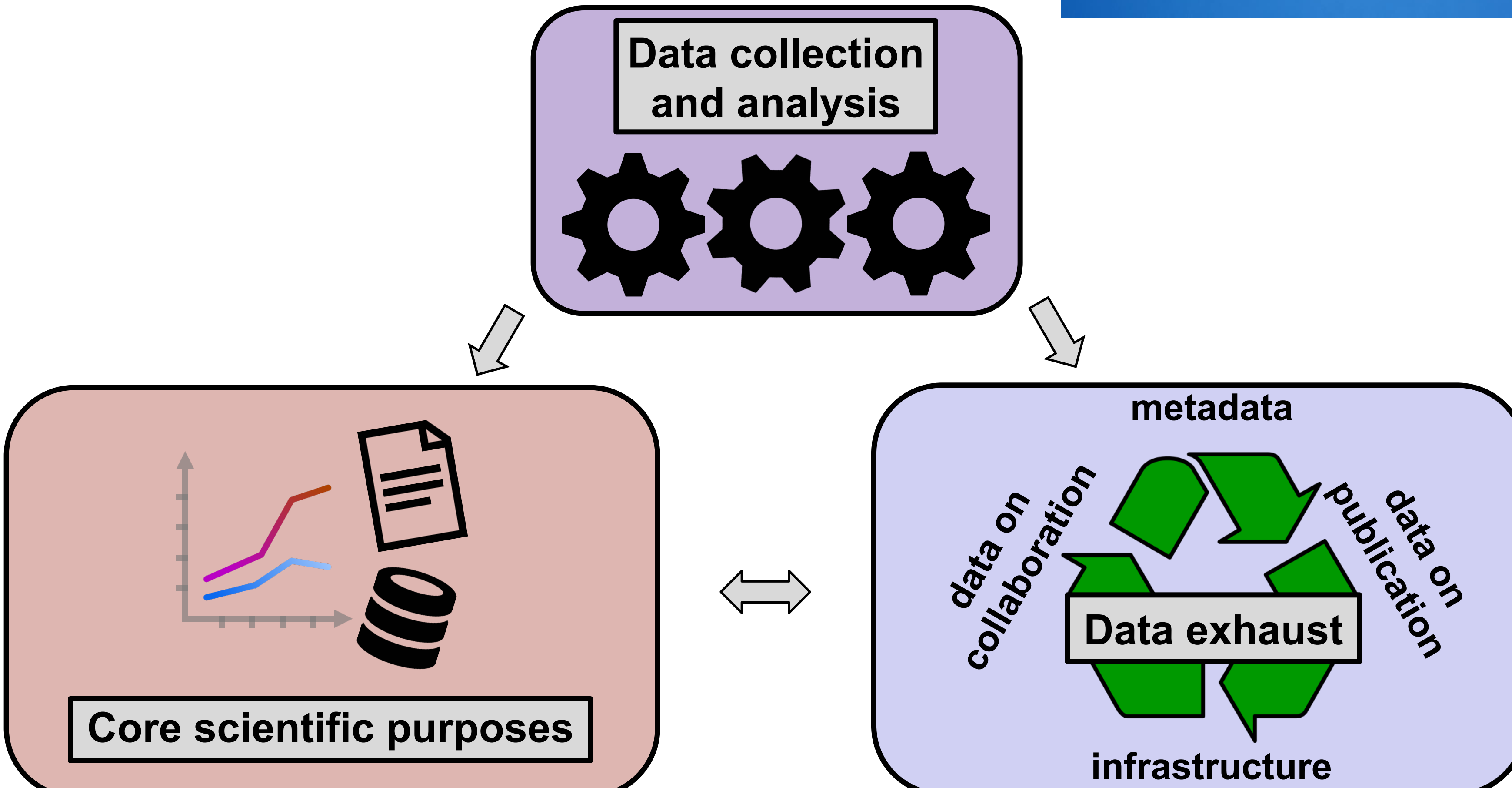
The Other Side of the Data Science Coin:

The Data Exhaust from Personal Genomics

(privacy & SOS)

Data Exhaust

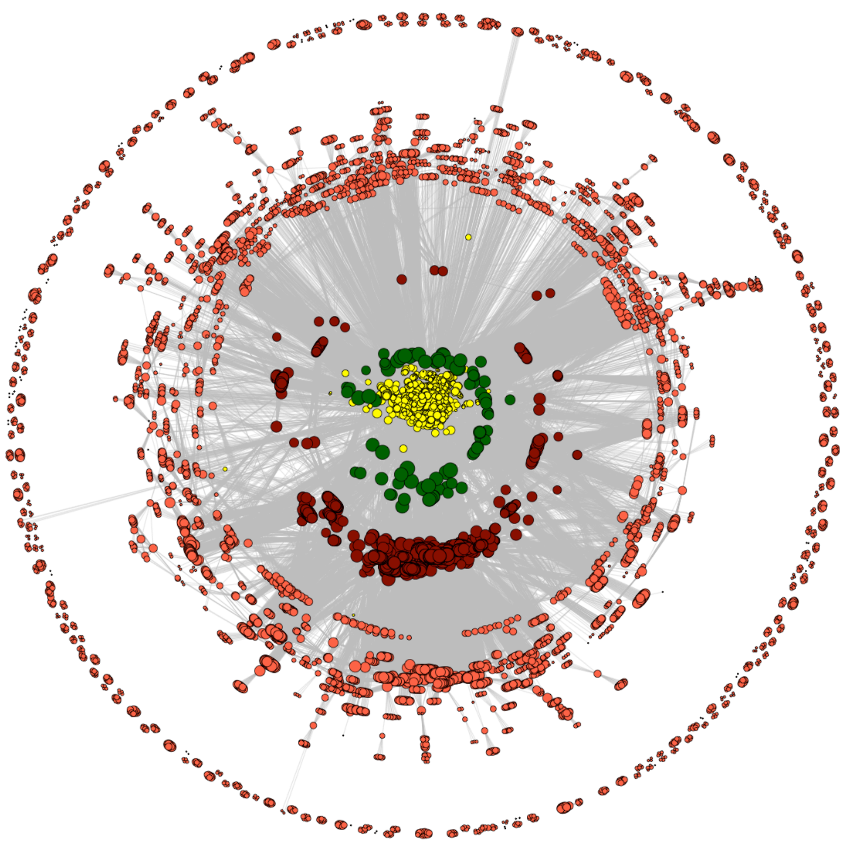
- Creative use of data is key to data science!
- Data exhaust = exploitable byproducts of big data collection and analysis



[photos: wikipedia/wikimedia]

Exhaust Mining Application: Using Science to Study Science (SOS)

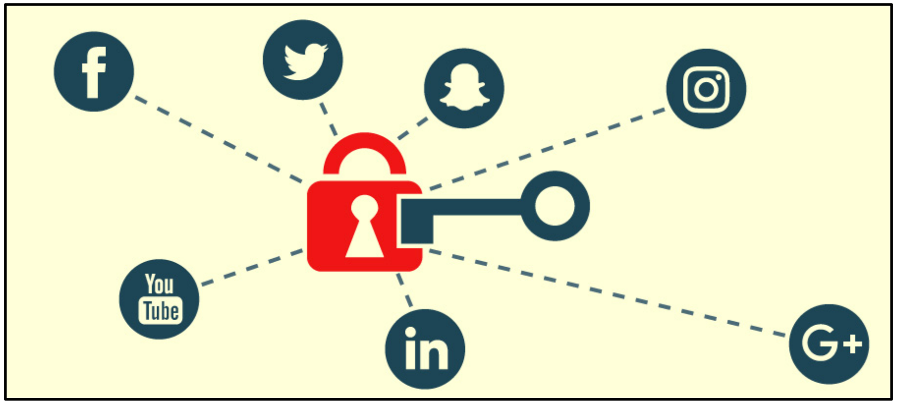
- ENCODE member
- non-member
- ENCODE member broker
- non-member broker
- co-authorship



- Mining output of science (Scientific Publications) to understand how science works as a social enterprise
- Co-authorship network of members of the human genome annotation group (ENCODE) & users of this groups data

[Wang et al., TIG ('16)]

Genomics has similar "Big Data" Dilemma as in the Rest of Society



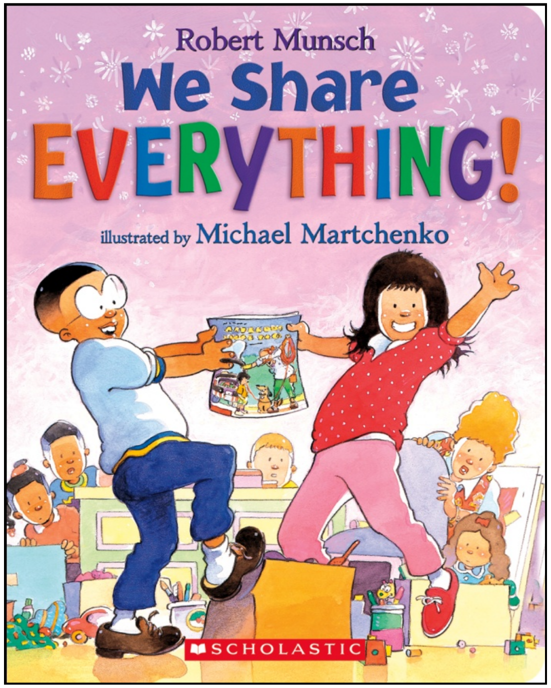
- We confront privacy risks every day we access the internet (e.g., social media, e-commerce).
- Sharing & "peer-production" is central to success of many new ventures, with analogous risks to genomics
  - **EG web search**: Large-scale mining essential

Genetic Exceptionalism :
The Genome is very fundamental data, potentially very revealing about one's identity & characteristics

Personal Genomic info. essentially meaningless currently but will it be in 20 yrs? 50 yrs?
Genomic sequence very revealing about one's children. Is true consent possible?
Once put on the web it can't be taken back

Ethically challenged history of genetics
Ownership of the data & what consent means (Hela)
Could your genetic data give rise to a product line?

[Seringhaus & Gerstein ('09), *Hart. Courant* (Jun 5); Greenbaum & Gerstein ('11), *NY Times* (6 Oct), D Greenbaum & M Gerstein ('08). Am J. Bioethics; D Greenbaum & M Gerstein, Hartford Courant, 10 Jul. '08 ; SF Chronicle, 2 Nov. '08; Greenbaum et al. *PLOS CB* ('11) ; Greenbaum & Gerstein ('13), The Scientist; Photos from NY Times, it.wisc.edu]

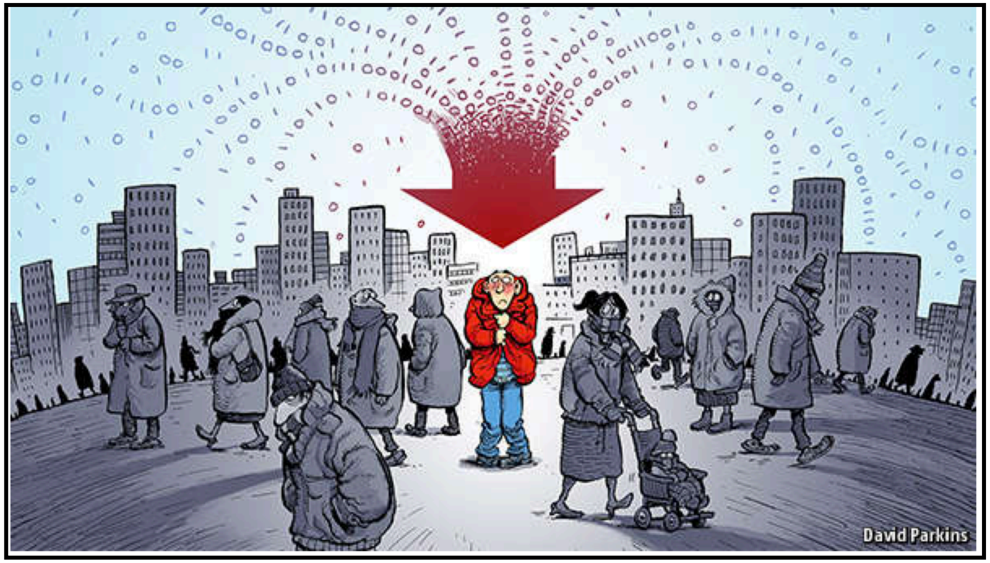


The Other Side of the Coin: Why we should share

- Sharing helps **speed research**
  - Large-scale mining of this information is important for medical research
  - Statistical power
  - Privacy is cumbersome, particularly for big data

The Dilemma

- The individual (harmed?) v the collective (benefits)
  - But do sick patients care about their privacy?
- How to balance risks v rewards
  – Quantification



[Economist, 15 Aug '15]

[Yale Law Roundtable ('10). Comp. in Sci. & Eng. 12:8; D Greenbaum & M Gerstein ('09). Am. J. Bioethics; D Greenbaum & M Gerstein ('10). SF Chronicle, May 2, Page E-4; Greenbaum et al. *PLOS CB* ('11)]

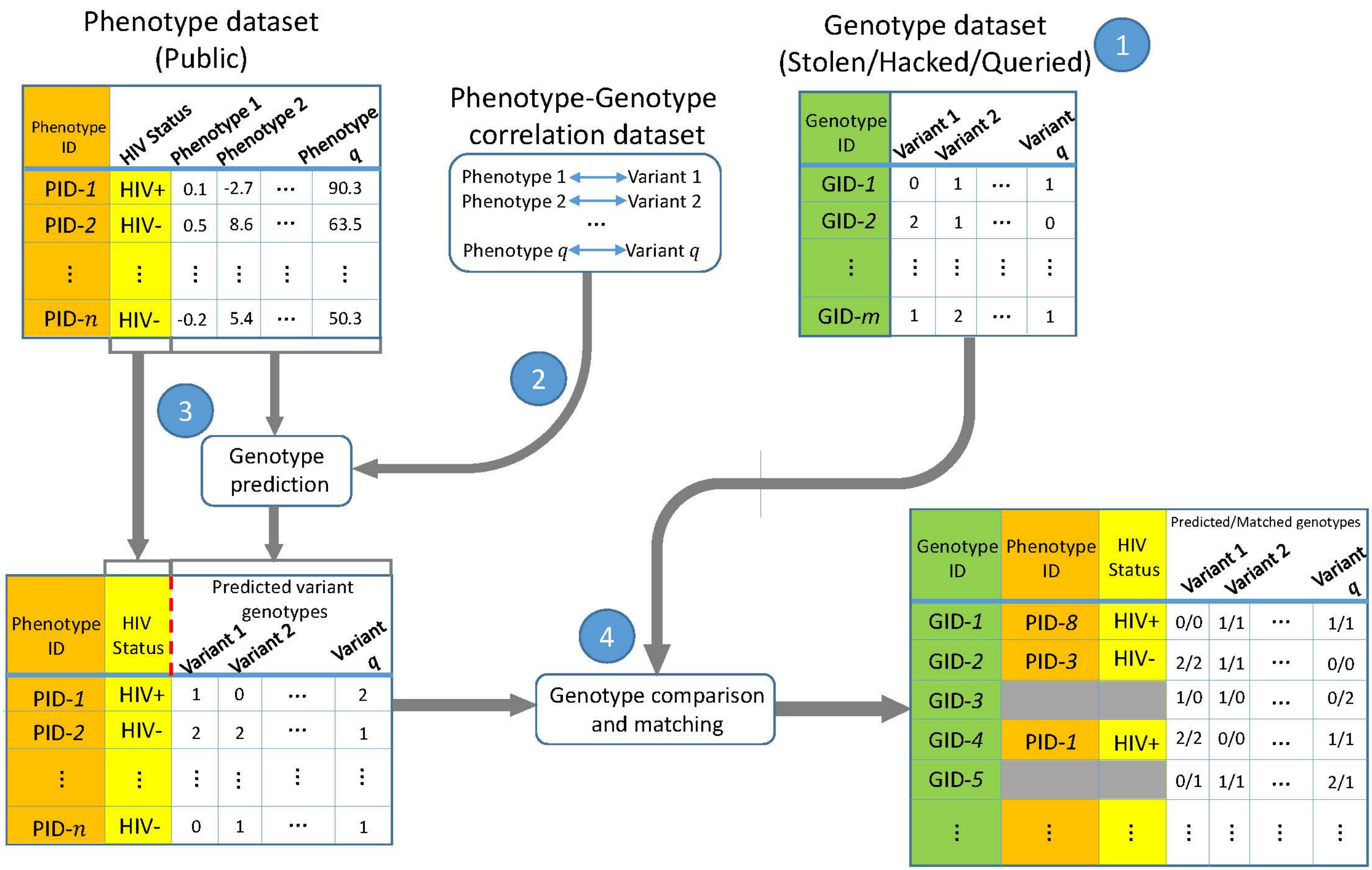
Current Social & Technical Solutions: The quandary where are now

- **Closed Data** Approach
  - Consents
  - "Protected" distribution via dbGAP
  - Local computes on secure computer
- Issues with Closed Data
  - Non-uniformity of consents & paperwork
    - Different, confusing int'l norms
  - Computer security is burdensome
  - Many schemes get "hacked" .
  - **Tricky aspects of high-dimensional data** (ease of creating quasi-identifiers)

- **Open Data**
  - Genomic "test pilots" (ala PGP)?
    - Sports stars & celebrities?
  - Some public data & data donation is helpful but is this a realistic solution for an unbiased sample of ~1M

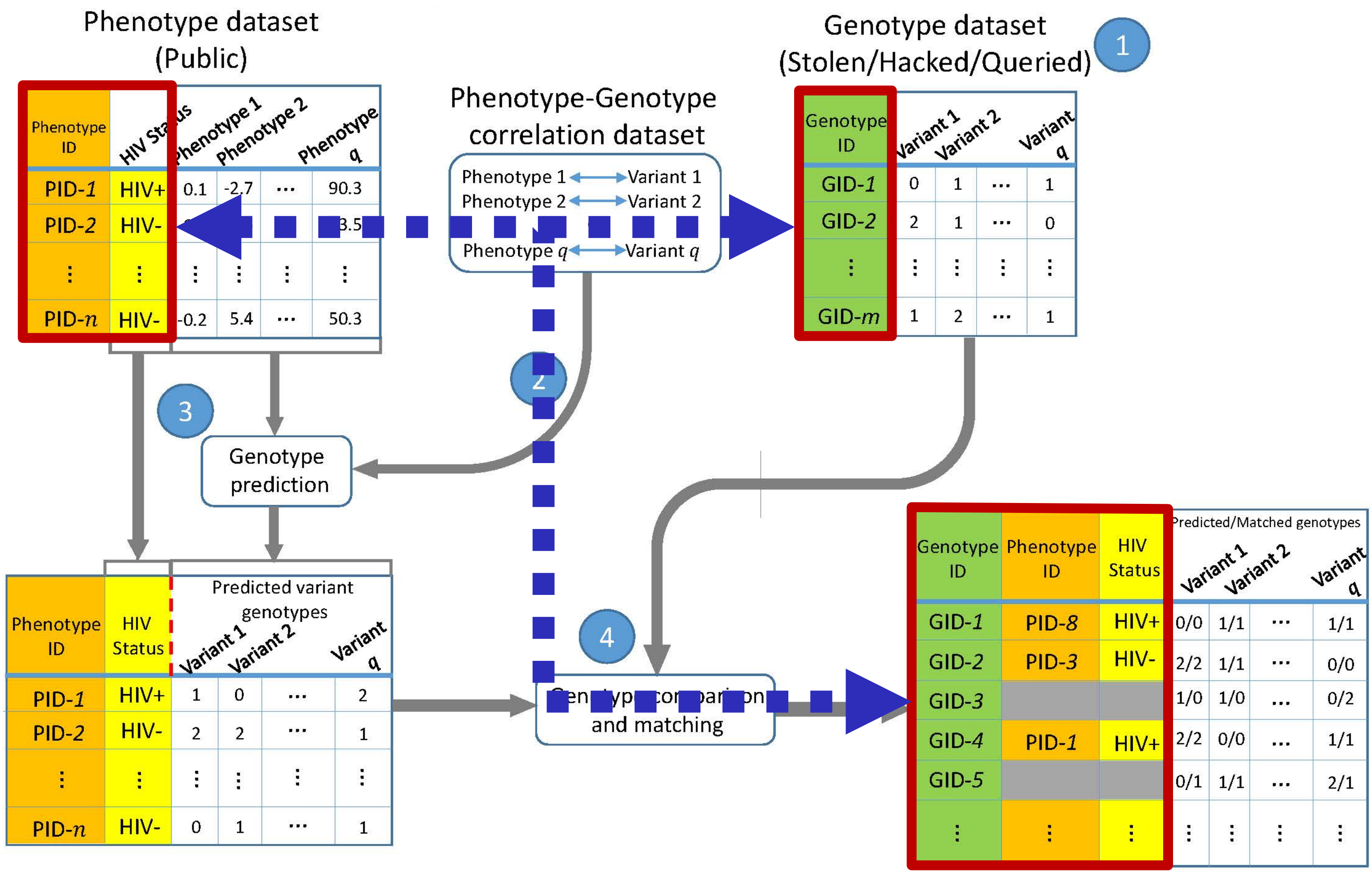
[Greenbuam et al ('04), Nat. Biotech; Greenbaum & Gerstein ('13), The Scientist; Photo: futurism.com]

Linking Attack Scenario



[Harmanciet al. Nat. Meth. (in revision)]

Linking Attack Scenario



[Harmanciet al. Nat. Meth. (in revision)]

Linking Attacks: Case of Netflix Prize

NETFLIX

IMDb

Names available for many users!

User (ID)	Movie (ID)	Date of Grade	Grade [1,2,3,4,5]
NTFLX-0	NTFLX-19	10/12/2008	1
NTFLX-1	NTFLX-116	4/23/2009	3
NTFLX-2	NTFLX-92	5/27/2010	2
NTFLX-1	NTFLX-666	6/6/2016	5
…	…	…	…
…	…	…	…

User (ID)	Movie (ID)	Date of Grade	Grade [0-10]
IMDB-0	IMDB-173	4/20/2009	5
IMDB-1	IMDB-18	10/18/2008	0
IMDB-2	IMDB-341	5/27/2010	-
…	…	…	…
…	…	…	…
…	…	…	…

- Many users are shared
- The grades of same users are correlated
- A user grades one movie around the same date in two databases

Anonymized Netflix Prize Training Dataset made available to contestants

Linking Attacks: Case of Netflix Prize

Names available for many users!

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…	…	…	…
…	…	…	…
…	…	…	…

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- IMDB users are public

- NetFLIX and IMdB moves are public

Linking Attacks: Case of Netflix Prize

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