

# Contemporary Genomics and Precision Health

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Eric Boerwinkle

Houston

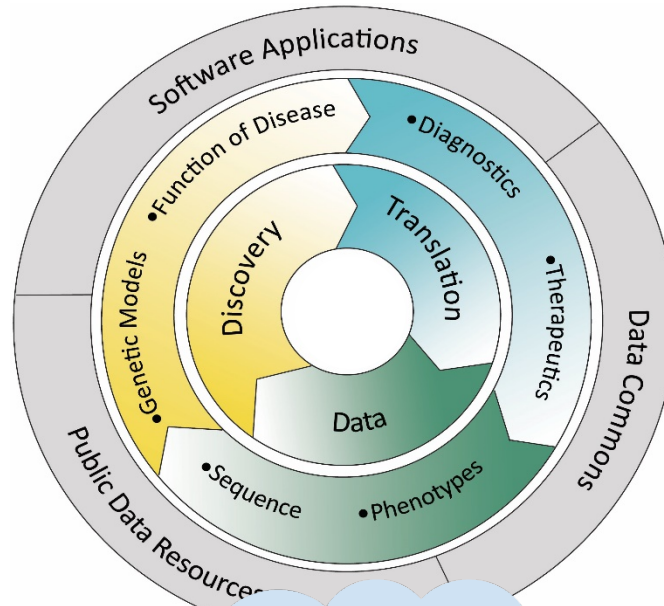
Oct 22, 2018



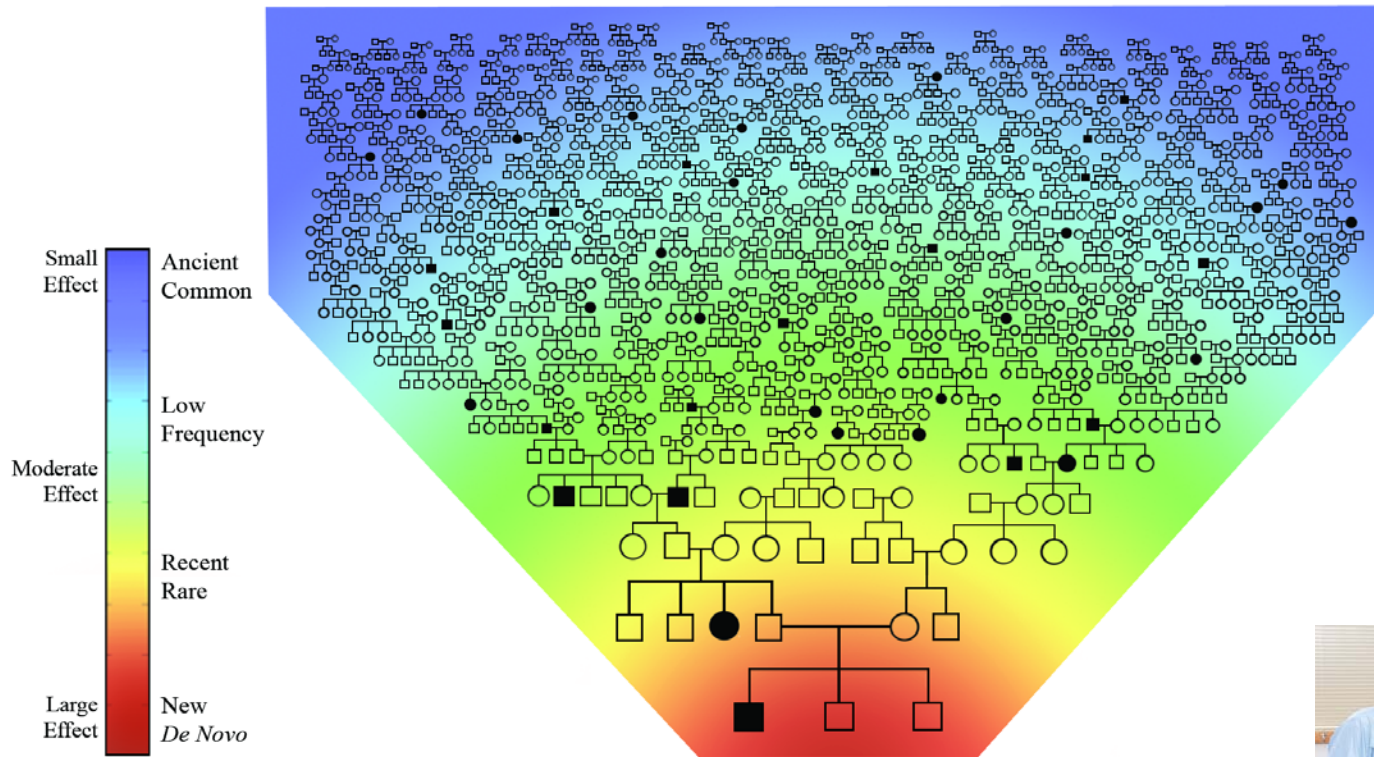
# Clinical ↔ Research Enterprises

**The New York Times**  
ON THE WEB

**DNA Test for Rare Disorders Becomes More Routine,**  
G. Kolata

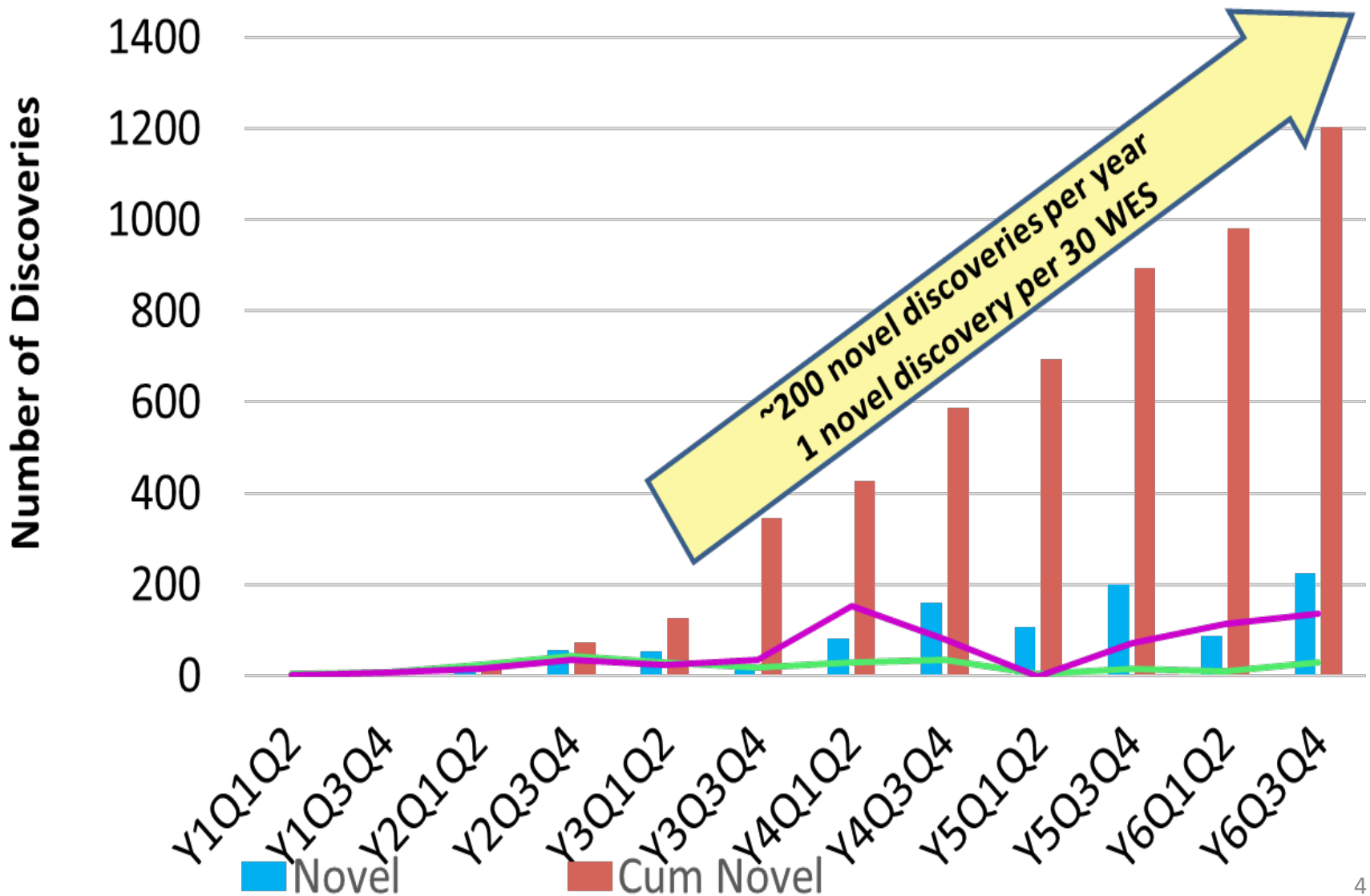


# Genomics in a Historic Context

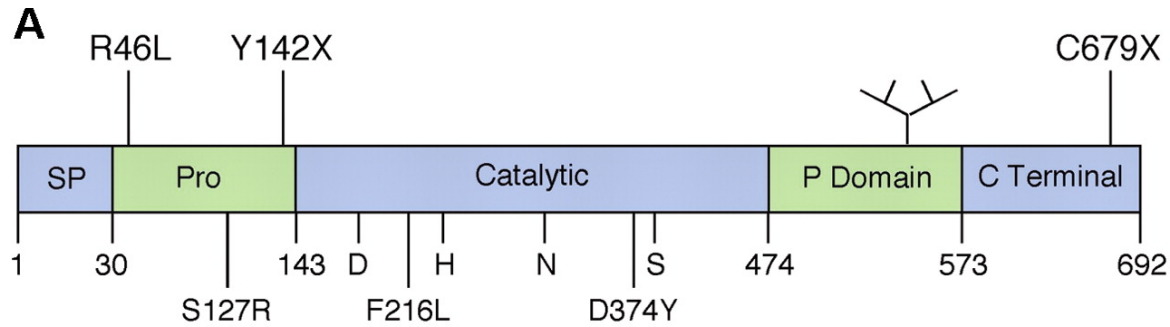


Lupski et al (2011) Cell

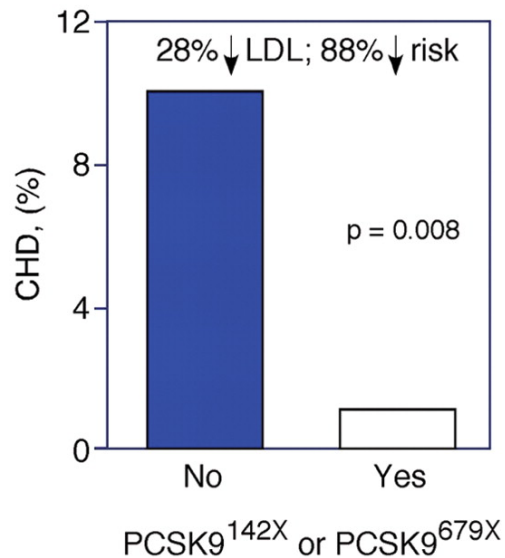
# Cumulative CMG Disease Gene Discovery



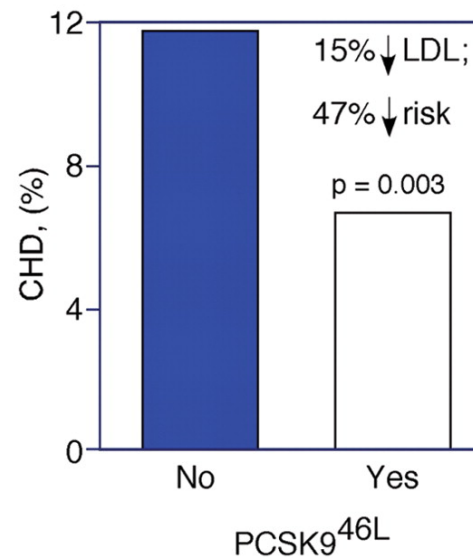
# PCSK9 schematic of nonsense mutations associated with low LDL cholesterol



**B** Y142X or C679X variants  
African-Americans  
N = 3,363 followed 15 years



R46L variant  
European-Americans  
N = 9,524 followed 15 years



*“Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals.” Barack Obama, 2015*

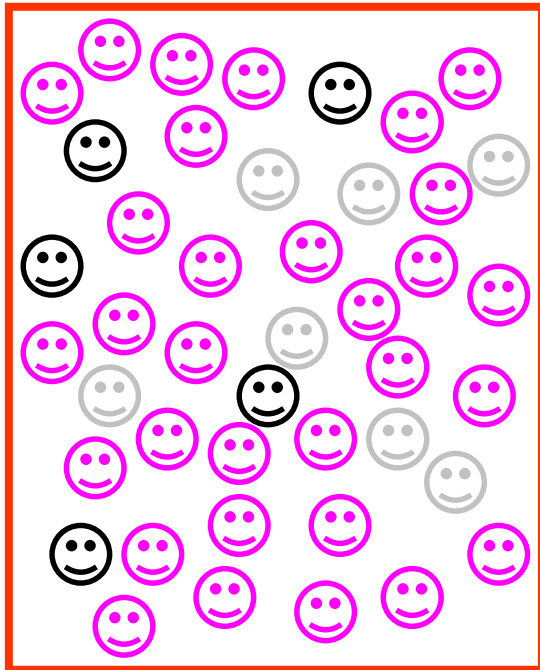
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# People react differently to drugs

“One size does not fit all ...”

- ☹️ Toxic responders
- 😐 Non-responders
- 😊 Responders



Patient population with same disease phenotype

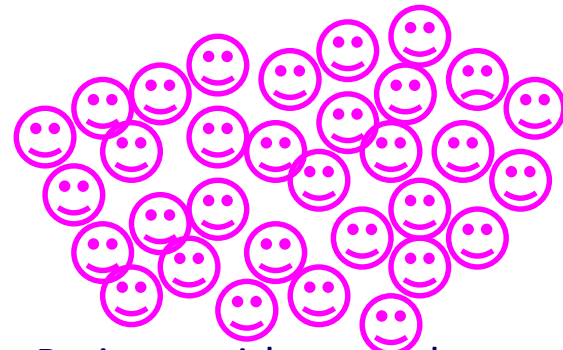
Genotyping



Patients with drug toxicity

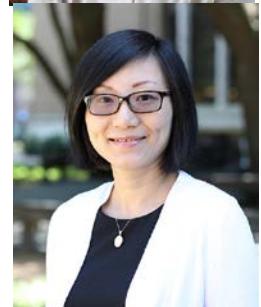
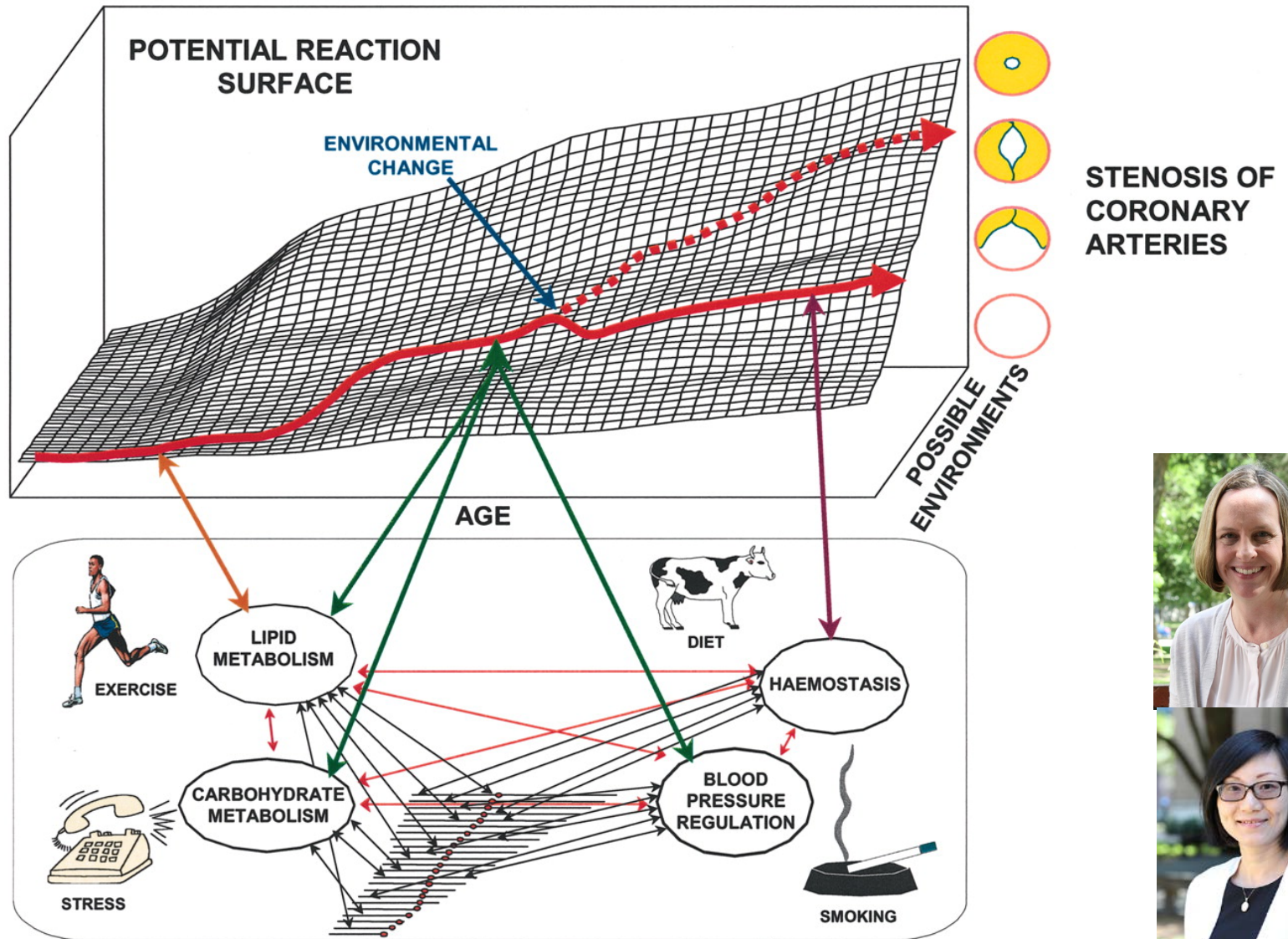


Patients with non-response to drug therapy



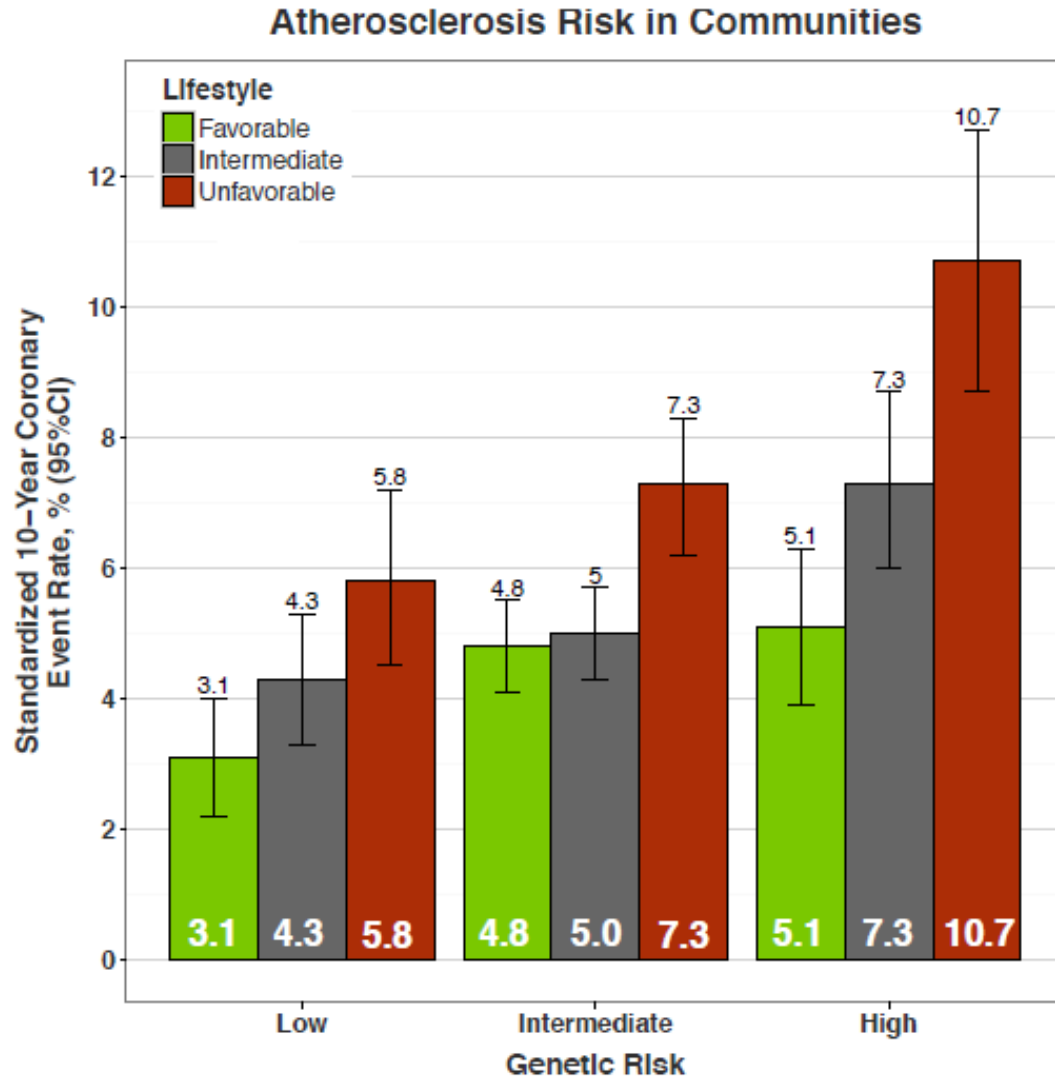
Patients with normal response to drug therapy

# Genes, Environments and Time





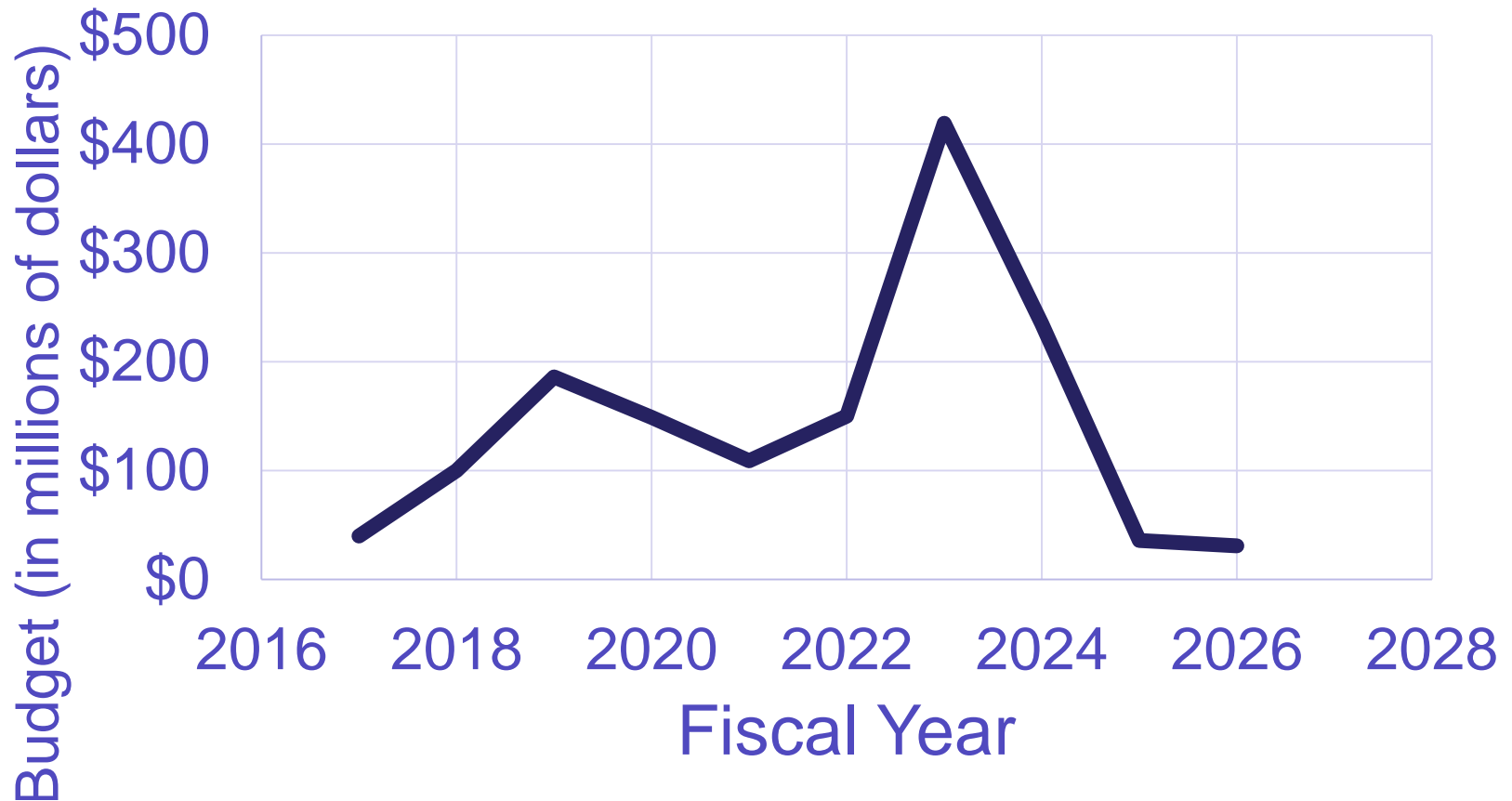
# Genes & Life Style & Risk



## Funds for *All of Us* Research Program under the 21<sup>st</sup> Century Cures Act

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### Appropriations for *All of Us* Research Program under the Cures Act



# All of Us Mission and Objectives

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## Nurture relationships

with one million or more participant partners, from all walks of life, for decades



## Our mission

To accelerate health research and medical breakthroughs, enabling individualized prevention, treatment, and care for all of us

Deliver one of the largest, richest biomedical datasets ever

that is easy, safe, and free to access



## Catalyze the robust ecosystem

of researchers and funders hungry to use and support it



# Version 1 is a “Get Started” Foundational Protocol

## Underway Now



### Enroll, Consent & EHR

- Recruit 18+ years old initially; plan to include children in next iteration
- eConsent or paper long-form
- Participants complete additional authorization to share EHR data



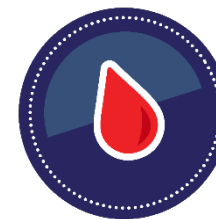
### Survey s

- Three initial participant provided information modules: The Basics, Overall Health, & Lifestyle



### Physical Measurements

- Blood pressure
- BMI
- Heart rate
- Height
- Hip circumference
- Waist circumference
- Weight

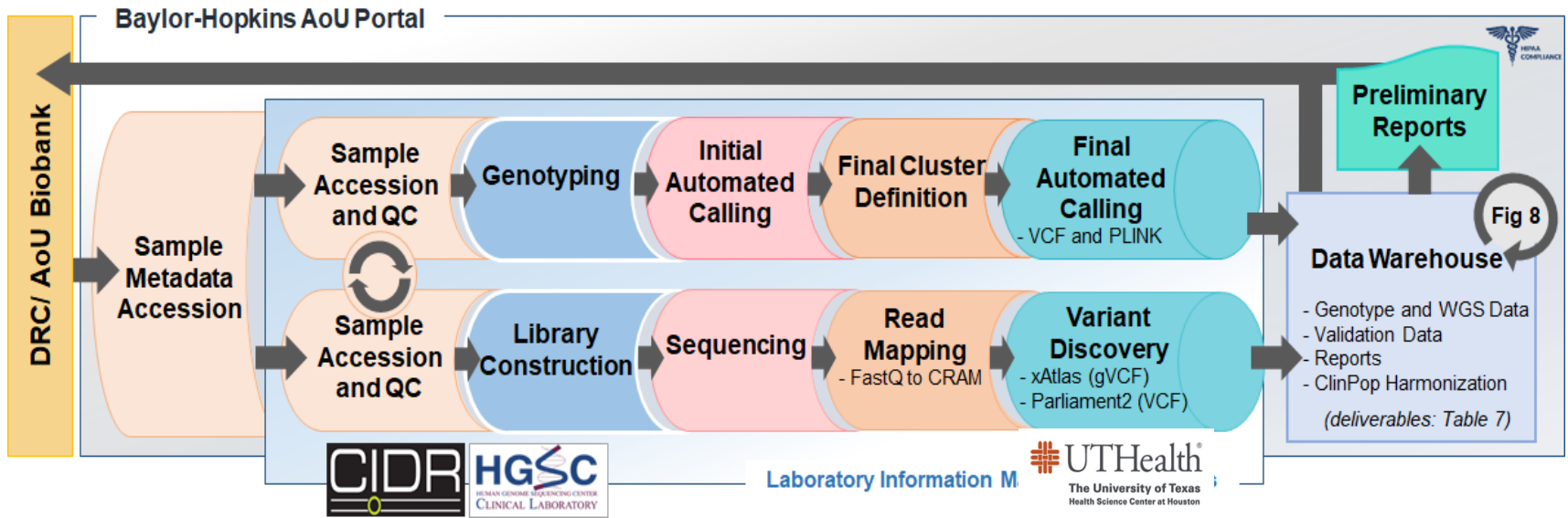


### Biosample s

- Blood (or saliva, if blood draw is unsuccessful)
- Urine
- 28 aliquots of blood and 6 of urine stored in Biobank

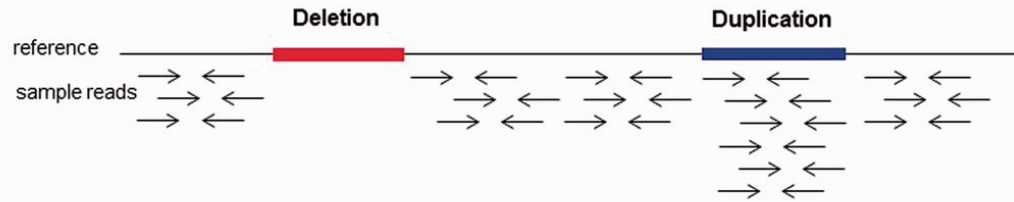


## Workflow Details : From Samples to Data

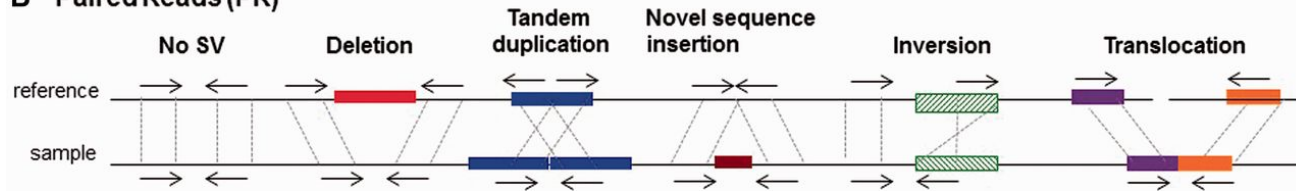


# Structural Variant Discovery

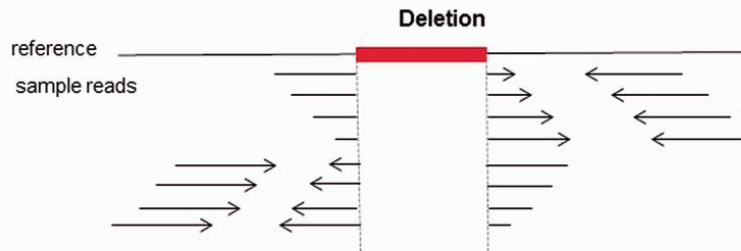
## A Read Depth (RD)



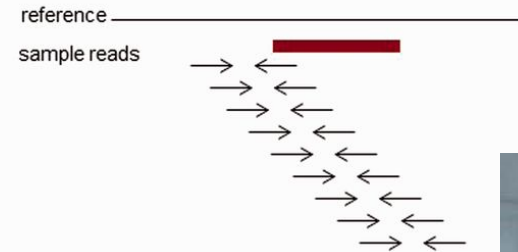
## B Paired Reads (PR)



## C Split Reads (SR)



## D. De Novo Assembly (AS)



# HGSC+UT Structural Variation At Scale



Engler et al. BMC Genomics (2019) 16:36  
 DOI: 10.1186/s12854-019-0474-3

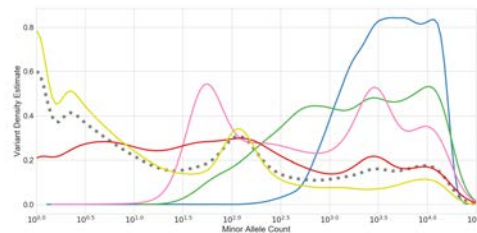


## DNA<sub>n</sub>exus

Open Access

Functional equivalence of genome sequencing analysis pipelines enables harmonized variant calling across human genetics projects

Allison A. Regier, Yossi Farjoun, David Larson, Olga Krashenina, Hyun Min Kang, Daniel P. Howrigan, Bo-Juen Chen, Manisha Kher, Eric Banks, Darren C. Ames, Adam C. English, Heng Li, Jinchuan Xing, Yeting Zhang, Tara Matise, The NHLBI Trans-Omics for Precision Medicine (TOPMed) Program, Goncalo R. Abecasis, Will Salerno, Michael C. Zody, Benjamin M. Neale, Ira M. Hall  
 doi: <https://doi.org/10.1101/269316>



### Parliament2: Fast Structural Variant Calling Using Optimized Combinations of Callers

Samantha Zarate, Andrew Carroll, Olga Krashenina, Fritz J Sedlazeck, Goo Jun, William Salerno, Eric Boerwinkle, Richard Gibbs

doi: <https://doi.org/10.1101/424267>

This article is a preprint and has not been peer-reviewed [what does this mean?]

**HS1011 Personal Genome SVs**  
(N=1)

**NIH GRCh38 WGS Protocol**  
(N=350)

**CVD F1**  
(N=16,423)

**CVD F2**  
(N=35,239)

**TOPMed SVs**  
(N=100,000+)

2015

2016

2017

2018

2019

**ADSP Family WGS Parliament**  
(N=584)

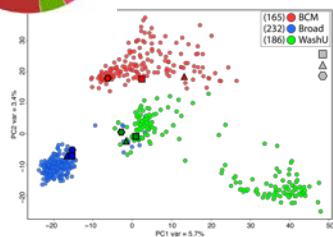
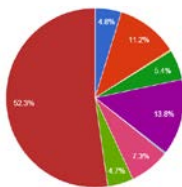
**CCDG F1**  
(N=22,609)

**TOPMed Bakeoff**  
(N=756)

**CCDG F2**  
(N=55,000)

**All of Us Y1**  
(N=7,000 CAP/CLIA)

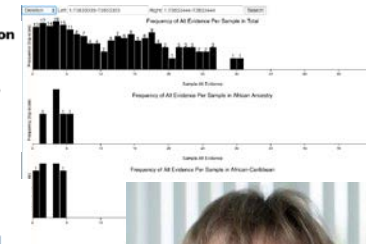
- Breakdancer
- CNVnator
- Crest
- Delly
- Pindel
- SV-Stat
- Tiresias
- Spiral
- Multi-Program



### xAtlas: Scalable small variant calling across heterogeneous next-generation sequencing experiments

Jesse Farek, Daniel Hughes, Adam Mansfield, Olga Krashenina, Waleed Nasser, Fritz J Sedlazeck, Ziad Khan, Eric Vanner, Ginger Metcalf, Eric Boerwinkle, Donna M Pluzny, Richard A Gibbs, William Salerno  
 doi: <https://doi.org/10.1101/295071>

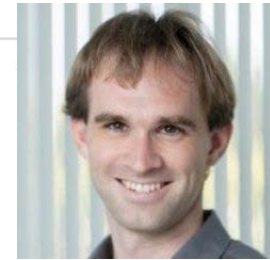
This article is a preprint and has not been peer-reviewed [what does this mean?]



### GLnexus: joint variant calling for large cohort sequencing

Michael F Lin, Ohad Rodeh, John Penn, Xiaodong Bai, Olga Krashenina, William J Salerno, Jeffrey G Reid  
 doi: <https://doi.org/10.1101/343970>

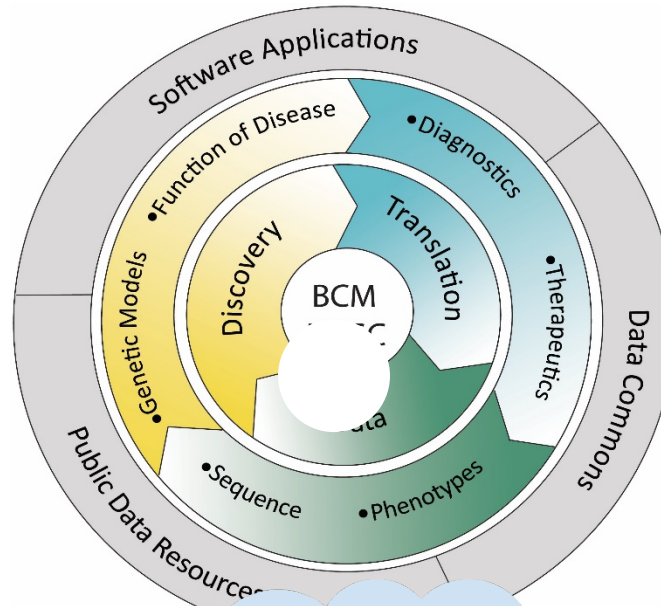
This article is a preprint and has not been peer-reviewed [what does this mean?]



# Clinical ↔ Research Enterprises

**The New York Times**  
ON THE WEB

**DNA Test for Rare Disorders Becomes More Routine,**  
G. Kolata





# UTHealth School of Public Health: Who are we?

**\$48** Million in research expenditures (78% Federal)



**148** Exceptional Faculty

51 Professors  
56 Associate Prof  
41 Assistant Prof

**1,288**

Students being trained from 53 countries in how to prevent disease and improve outcomes.



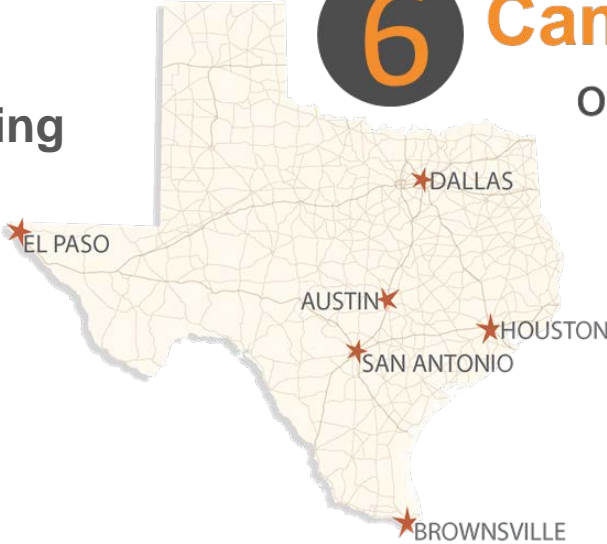
in the US for training medical students public health



**Foster disease prevention in the Hispanics** by cohort development and becoming integral in that community.  
More than 150,000 examinations.



**6** Campuses one school



# Research Excellence

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Genetic Analysis  
and Bioinformatics



Health Promotion &  
Behavioral Sciences



Hispanic Health



Health Services Data