DNA Test for Rare Disorders Becomes More Routine,
G. Kolata
Genomics in a Historic Context

Cumulative CMG Disease Gene Discovery

~200 novel discoveries per year
1 novel discovery per 30 WES
PCSK9 schematic of nonsense mutations associated with low LDL cholesterol

A

B

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

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

CHD, (%)  

28% ↓ LDL; 88% ↓ risk

p = 0.008

CHD, (%)  

15% ↓ LDL; 47% ↓ risk

p = 0.003
“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
People react differently to drugs

“One size does not fit all …”

Patient population with same disease phenotype

Genotyping

- Toxic responders
- Non-responders
- Responders

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

Atherosclerosis Risk in Communities

Data from Khera et al, (NEJM)
Funds for *All of Us* Research Program under the 21st Century Cures Act

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

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>Budget (in millions of dollars)</th>
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<tr>
<td>2016</td>
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<tr>
<td>2018</td>
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All of Us Mission and Objectives

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

Catalyze the robust ecosystem
of researchers and funders hungry to use and support it

Deliver one of the largest, richest biomedical datasets ever that is easy, safe, and free to access
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
- Three initial participant provided information modules: The Basics, Overall Health, & Lifestyle

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

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

Full protocol at allofus.nih.gov.
Workflow Details: From Samples to Data
Structural Variant Discovery

A. Read Depth (RD)
- Reference
- Sample reads
- Deletion
- Duplication

B. Paired Reads (PR)
- No SV
- Deletion
- Tandem duplication
- Novel sequence insertion
- Inversion
- Translocation

C. Split Reads (SR)
- Reference
- Sample reads
- Deletion

D. De Novo Assembly (AS)
- Reference
- Sample reads

Escaramis, 2015 (PMID: 25877305)
Assessing structural variation in a personal genome—towards a human reference diploid genome

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

- 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+)
- 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)
Clinical ↔ Research Enterprises

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

$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.

#1 in the US for training medical students public health

6 Campuses
- EL PASO
- DALLAS
- AUSTIN
- SAN ANTONIO
- HOUSTON
- BROWNSVILLE

UTHealth School of Public Health: Who are we?
Research Excellence

Genetic Analysis and Bioinformatics

Health Promotion & Behavioral Sciences

Hispanic Health

Health Services Data