The *All of Us* Research Program

Geoffrey Ginsburg, MD, PhD
Chief Medical and Scientific Officer, *All of Us* Research Program

Clinical Center Research Hospital Board
June 21st, 2024

National Institutes of Health

76th Anniversary
Framingham Heart Study

Factors of Risk in the Development of Coronary Heart Disease—
Six-Year Follow-up Experience

The Framingham Study

WILLIAM B. KANNEL, M.D., THOMAS R. DAWBER, M.D., F.A.C.P.,
ABRAHAM KAGAN, M.D., F.A.C.P., NICHOLAS REVOTSKIE, M.D.,
AND JOSEPH STOKES, III, M.D.
Framingham, Massachusetts

INCREASINGLY RELIABLE ESTIMATES of the prevalence and incidence of coronary heart disease (CHD) emphasize the importance of this disease as a contemporary health hazard. Cardiovascular disease is now the lea
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Since it has been established that coronary atherosclerosis is present for many years prior to the development of symptomatic CHD, it seems evident that efforts at prevention must begin many years before the

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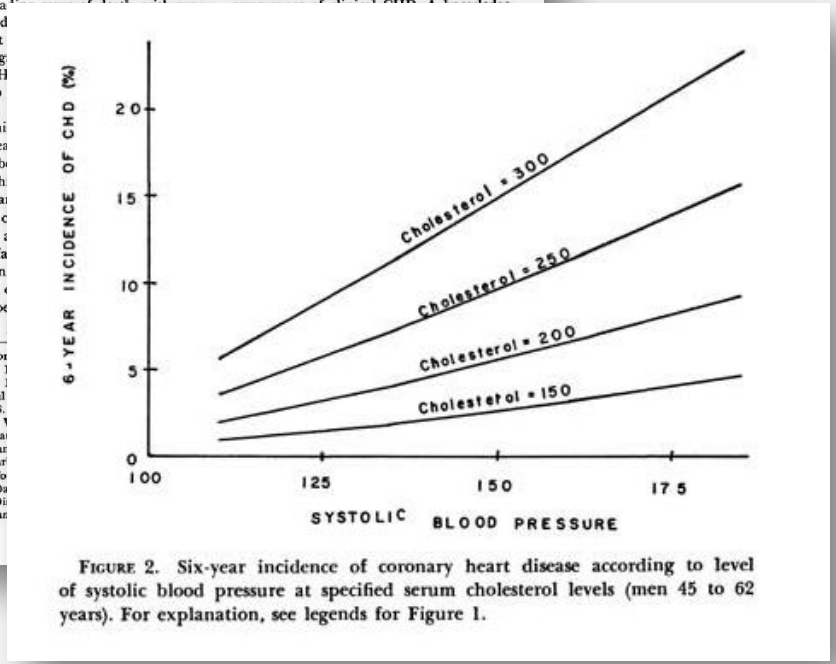


FIGURE 2. Six-year incidence of coronary heart disease according to level of systolic blood pressure at specified serum cholesterol levels (men 45 to 62 years). For explanation, see legends for Figure 1.

Enrolled 5,209 men and women in 1948

Some Framingham early discoveries:

- 1960 – Cigarettes increase heart disease
- 1961 – cholesterol, blood pressure increase heart disease
- 1967 – exercise decreases risk of heart disease; obesity increases it
- 1970 – high blood pressure and atrial fibrillation cause stroke

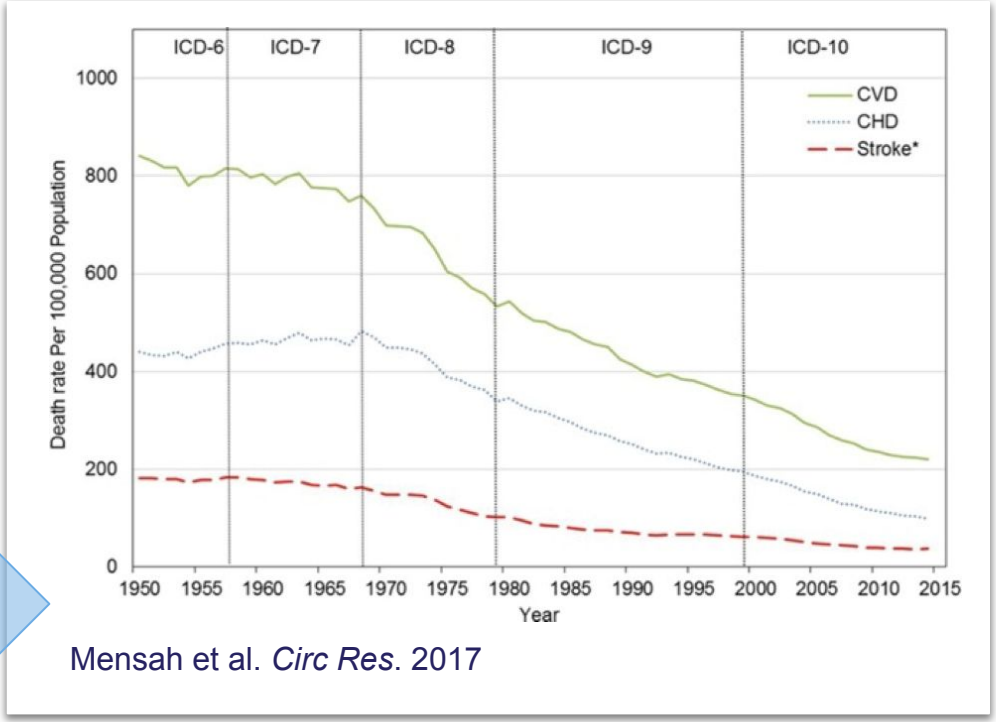
Kannel et al. Annals of Intern Med, 1961

The Strength of Large Cohort Studies

The impact of Framingham (and similar cohorts) has been dramatic

From 1950 - 1996: Heart disease mortality fell 56%, stroke rates fell by 70%

Since 1990, heart disease mortality has continued to fall by 22%



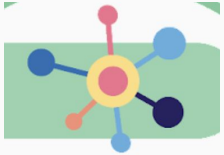
Mensah et al. *Circ Res*. 2017

The *All of Us* Research Program

<u>Our Mission</u>: Accelerate health research and medical breakthroughs, enabling individualized prevention, treatment, and care of all of us

Nurture partnerships for decades with at least a **million participants** who reflect the diversity of the U.S.

Deliver one of the **largest**, **richest biomedical datasets** that is broadly available and secure.



Catalyze an ecosystem of **communities**, **researchers**, and **funders** who make *All of Us* an **indispensable** part of health research.

"The program's rich and diverse dataset is now a vital resource for medical researchers across the NIH, the country, and indeed the world."
- Dr. Monica Bertagnolli, Massachusetts Policymakers All of Us Briefing, April 2024

809K+ Participants Enrolled

Participant Enrollment

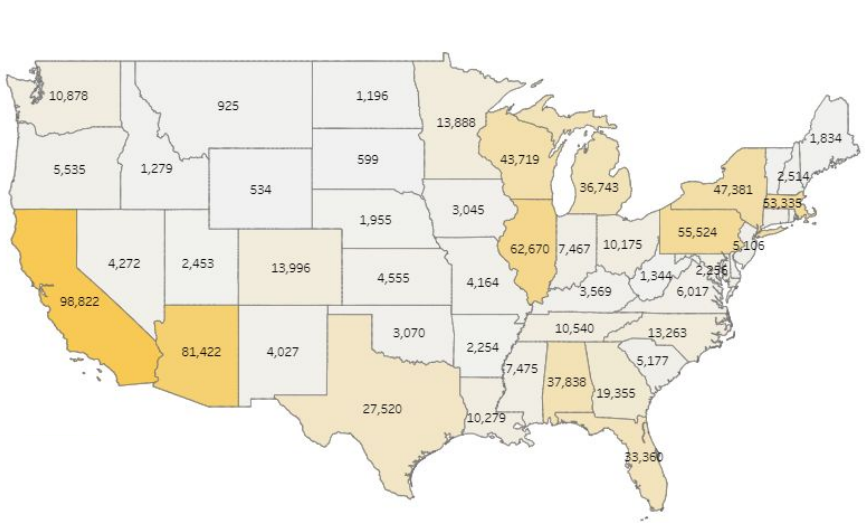
809,000+
Participants

450,000+
Electronic Health Records

553,000+
Participants who have completed initial steps of the program

572,000+
Biosamples

Map of Participants

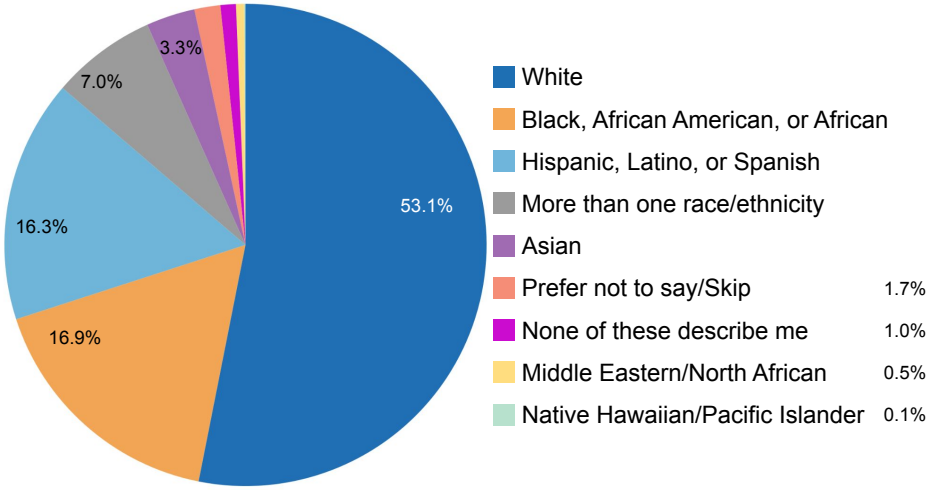


Plus >4,700 consented participants across U.S. territories

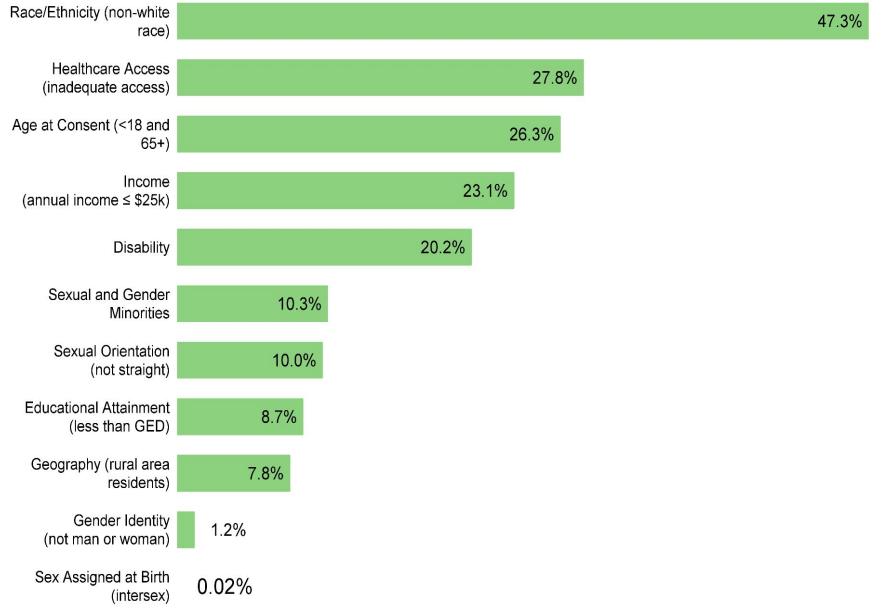
Over 87% of *All of Us* participants are underrepresented in biomedical research

Participant Diversity

Race & Ethnicity of Participants



UBR Category



Over 87% of *All of Us* participants are underrepresented in biomedical research

Numbers current as of May 1, 2024

Data Types Collected from *All of Us* Participants

Currently open to nearly all adults 18 and over living in the United States

Electronic Health Records

Data types collected from EHR include:

- Demographics
- Vital signs
- Diagnoses
- Procedures
- Medications
- Doctor and Laboratory Visits

Participant Surveys

- The Basics
- Overall Health
- Lifestyle
- Health Care Access & Utilization
- Personal and Family Medical History
- Social Determinants of Health
- Mental Health and Well-Being

Physical Measurements

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

Biosamples

- Blood
- Saliva
- Urine

Wearable Data

Fitbit data, including:

- Heart Rate
- Activity (Daily Summary)
- Activity Intraday Steps
- Sleep data

Nearly 250,000 Whole Genome Sequences Available to Advance Precision Medicine

The *All of Us* Researcher Workbench contains the one of the **largest sets of whole genome sequences widely available for research.**

413,350+
Survey Responses

337,500+
Physical Measurements

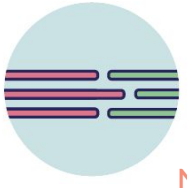
312,900+
Genotyping Arrays

287,000+
Electronic Health Records

245,350+
Whole Genome Sequences

11,350+
Structural Variants

NEW! In 2023



1,000+
Long-Read Sequences

NEW! In 2023

15,600+
Fitbit Records

NEW! Sleep Data

The whole genome sequence dataset includes variation at more than **1 billion** locations, which is nearly **one-third** of the entire human genome

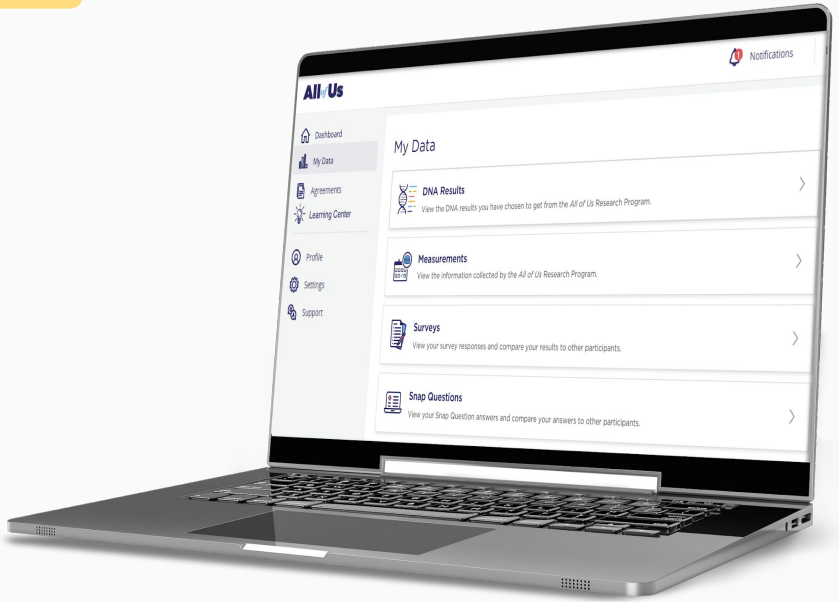
Includes 275 million genetic variants never seen before, including 4 million with protein coding consequences

Return of Value to *All of Us* Participants: A Unique Feature of *All of Us*

Return of Value for Participants

Participants may receive:

- ***Genetic information***
- Survey data (comparative)
- EHR and claims data
- Ongoing study updates
- Aggregate results
- Scientific findings
- Opportunities to be contacted for other research opportunities



Participants Can Receive Two Types of Health-Related Genetic Results

Hereditary Disease Risk (HDR) Report

All of Us looks for genetic variants in 59 genes associated with serious health conditions, including:

- Breast cancer
- Ovarian cancer
- Uterine cancer
- Colorectal cancer
- Prostate cancer
- Melanoma
- Brain cancer
- Pancreatic cancer
- Stomach cancer
- Familial hypercholesterolemia
- Cardiomyopathies
- Arrhythmias
- Arteriopathies
- Neurofibromatosis type 2

Medicine and Your DNA Report

All of Us analyzes seven genes that can affect how bodies process medicine and impacts which medication or what dosage you take. This report includes 50+ different medicines that may be impacted by your genetics, including:

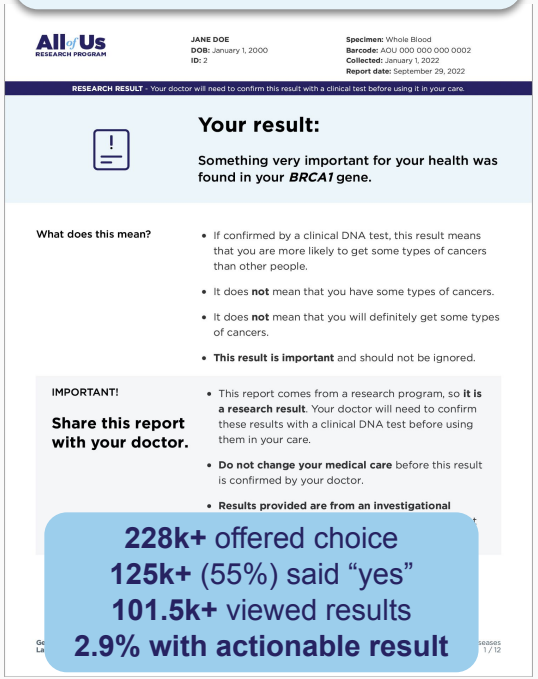
- Citalopram (Celexa®)
- Clopidogrel (Plavix®)
- Escitalopram (Lexapro®)
- Sertraline (Zoloft®)
- Lidocaine
- Glimepiride (Amaryl®)
- Sulfamethoxazole/ trimethoprim (Bactrim®)
- Simvastatin (Zocor®)
- Amitriptyline (Elavil®)

Genetic counselors (english and spanish) are available to help at any time

Genomic Health-Related Return of Results

Hereditary Disease Risk

All of Us currently looks for genetic variants in 59 genes associated with serious health conditions.



All of Us RESEARCH PROGRAM

JANE DOE
DOB: January 1, 2000
ID: 2

Specimen: Whole Blood
Barcode: AOU 000 000 000 0002
Collected: January 1, 2022
Report date: September 29, 2022

RESEARCH RESULT – Your doctor will need to confirm this result with a clinical test before using it in your care.

Your result:

Something very important for your health was found in your ***BRCA1*** gene.

What does this mean?

- If confirmed by a clinical DNA test, this result means that you are more likely to get some types of cancers than other people.
- It does **not** mean that you have some types of cancers.
- It does **not** mean that you will definitely get some types of cancers.
- **This result is important** and should not be ignored.

IMPORTANT!

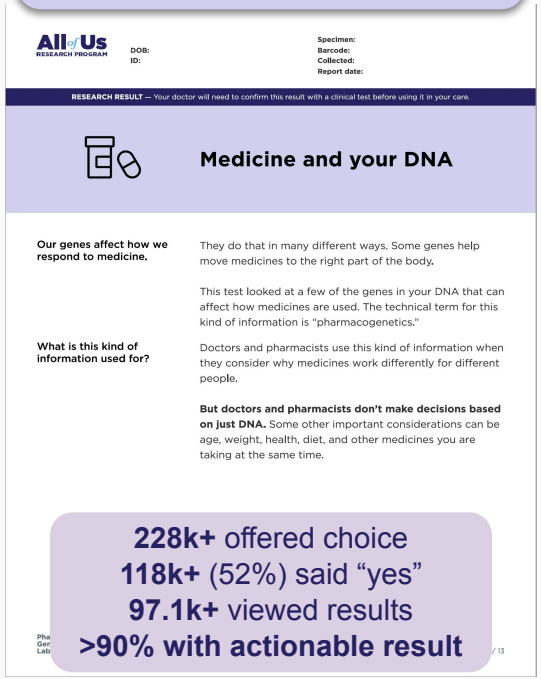
Share this report with your doctor.

- This report comes from a research program, so **it is a research result**. Your doctor will need to confirm these results with a clinical DNA test before using them in your care.
- **Do not change your medical care** before this result is confirmed by your doctor.
- **Results provided are from an investigational**

228k+ offered choice
125k+ (55%) said "yes"
101.5k+ viewed results
2.9% with actionable result

Medicine and Your DNA

All of Us analyzes seven genes that can affect how bodies metabolize medicines.



All of Us RESEARCH PROGRAM

DOB:
ID:

Specimen:
Barcode:
Collected:
Report date:

RESEARCH RESULT — Your doctor will need to confirm this result with a clinical test before using it in your care.

Medicine and your DNA

Our genes affect how we respond to medicine.

They do that in many different ways. Some genes help move medicines to the right part of the body.

This test looked at a few of the genes in your DNA that can affect how medicines are used. The technical term for this kind of information is "pharmacogenetics."

What is this kind of information used for?

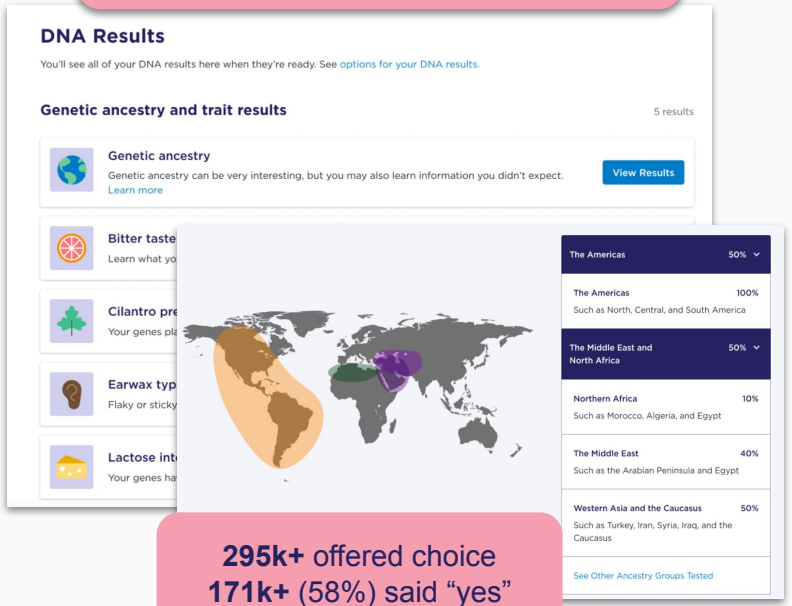
Doctors and pharmacists use this kind of information when they consider why medicines work differently for different people.

But doctors and pharmacists don't make decisions based on just DNA. Some other important considerations can be age, weight, health, diet, and other medicines you are taking at the same time.

228k+ offered choice
118k+ (52%) said "yes"
97.1k+ viewed results
>90% with actionable result

Genetic Ancestry and Traits

All of Us provides genetic ancestry details for 7 regions, and information on four genetic traits.



DNA Results

You'll see all of your DNA results here when they're ready. See options for your DNA results.

Genetic ancestry and trait results 5 results

Genetic ancestry
Genetic ancestry can be very interesting, but you may also learn information you didn't expect.
Learn more
View Results

Bitter taste
Learn what yo

Cilantro pre
Your genes pla

Earwax typ
Flaky or sticky

Lactose int
Your genes ha

The Americas 50%

The Americas 100%
Such as North, Central, and South America

The Middle East and North Africa 50%

Northern Africa 10%
Such as Morocco, Algeria, and Egypt

The Middle East 40%
Such as the Arabian Peninsula and Egypt

Western Asia and the Caucasus 50%
Such as Turkey, Iran, Syria, Iraq, and the Caucasus

See Other Ancestry Groups Tested

295k+ offered choice
171k+ (58%) said "yes"
168k+ viewed results

An Outcomes Research Agenda Downstream of Return of Results

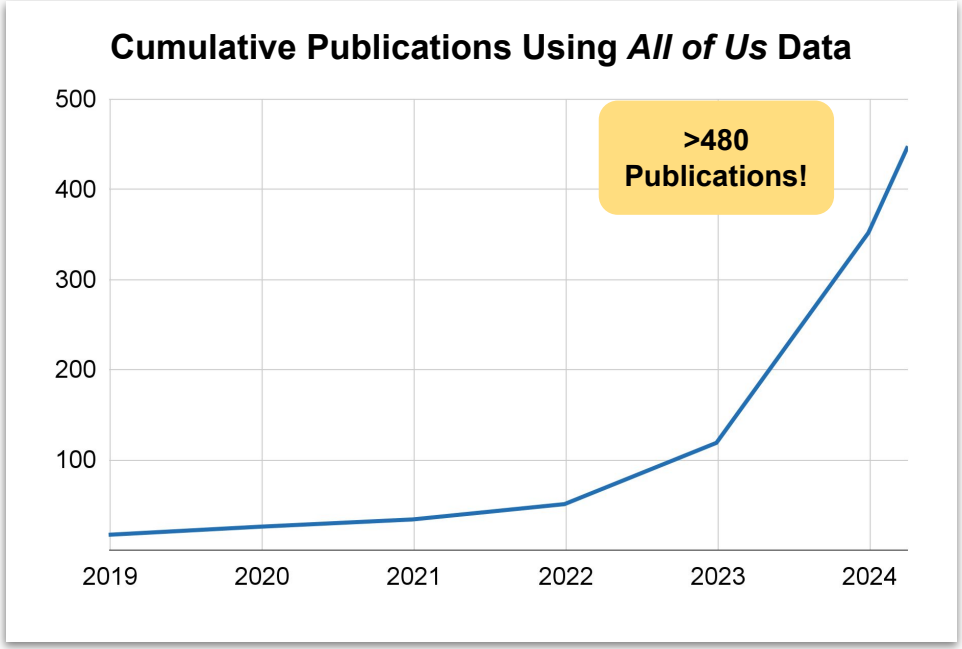
Measures under consideration with a focus on diverse populations:

- Understanding of the results
- Willingness and motivation to share
    - With family members
    - With health providers
- Influence on decisions
- Provider understanding of results
- Changes in management
- Follow up testing and evaluations
- Health care utilization
- Clinical utility
- Personal utility

Scientific Impact of *All of Us*

Growing Scientific Impact

researchallofus.org/publications/



Matching *All of* Us Participants with Actively-Recruiting Trials

All of Us RESEARCH PROGRAM

Electronic Health Records

181,529
***All of Us* Participants**

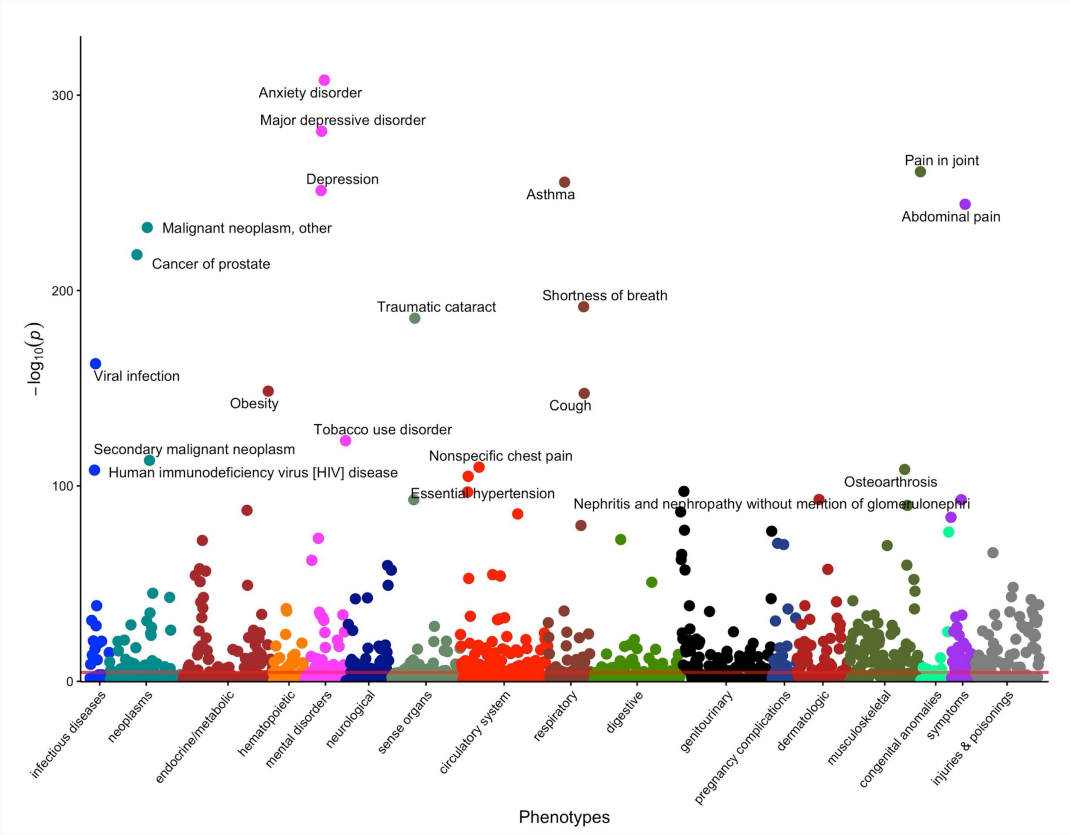
Match

1. Medical condition
2. Age
3. Sex at birth
4. Zip code

NIH *Database on clinical trials*
ClinicalTrials.gov

Actively recruiting, U.S.-based, adult trials

18,634
Clinical Trials



Shyr et al., JAMIA, 2024

Enabling Scientific Discovery with *All of Us*: What's Next?

Approaches to Collecting Environmental Data in *All of Us*

Data Linkages and Surveys

Location

Integrate locational information into the *All of Us* workbench through a decentralized address geocoding tool.

Center for Linkage and Acquisition of Data (CLAD)

Social Determinants of Health (2022)

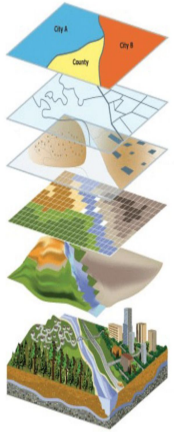
Environmental Exposure and Occupational Health (expected 2025)

Geospatial Data

Geographic Information System (GIS) Data Linkage

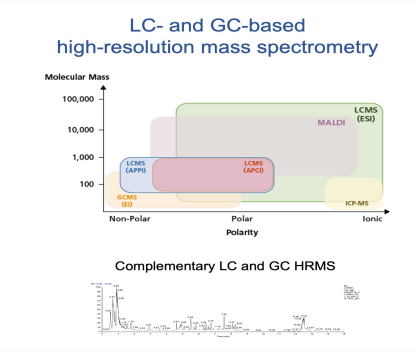
Growing Number of Data Layers

- Airports
- CAFOs
- Cellular towers
- Drinking water
- Dry cleaners
- Hazardous waste
- Highways
- Nuclear sites
- Wastewater
- Population info
- Power lines
- PR landfills
- Railroads
- Spills
- Sanitary landfills
- Superfund sites
- Toxic release sites,
- Etc.



Address at the time of survey completion and longest lived childhood address

Exposomics and Health



Untargeted HRMS (exposomics) through the **NIEHS** Human Health Exposure Analysis Resource to study **Type 2 Diabetes.**

Collaboration from other ICOs to tackle additional phenotypes.

Entire *All of Us* cohort

Subset of cohort

Ancillary Studies Will Have a Positive Impact on Increasing Access to a Research-Ready, Diverse National Cohort

Increasing complexity

Nutrition for Precision Health

Exploring the Mind

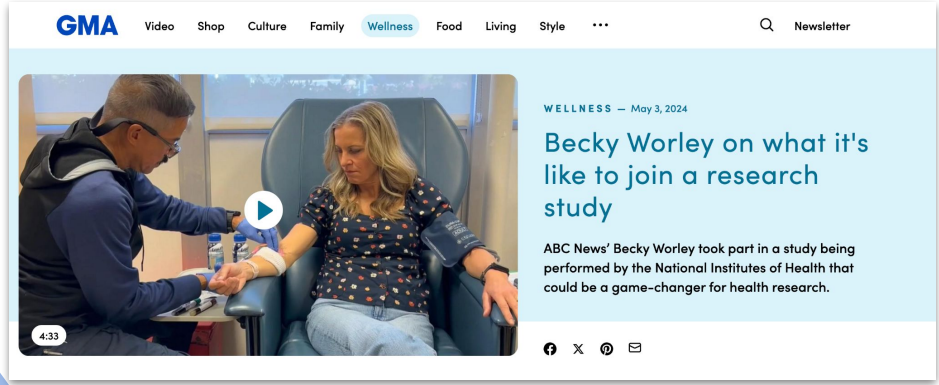
COVID Serology Study

Embedded studies

Recontact of participants for custom surveys, wearables, etc

Biospecimen use to generate new data

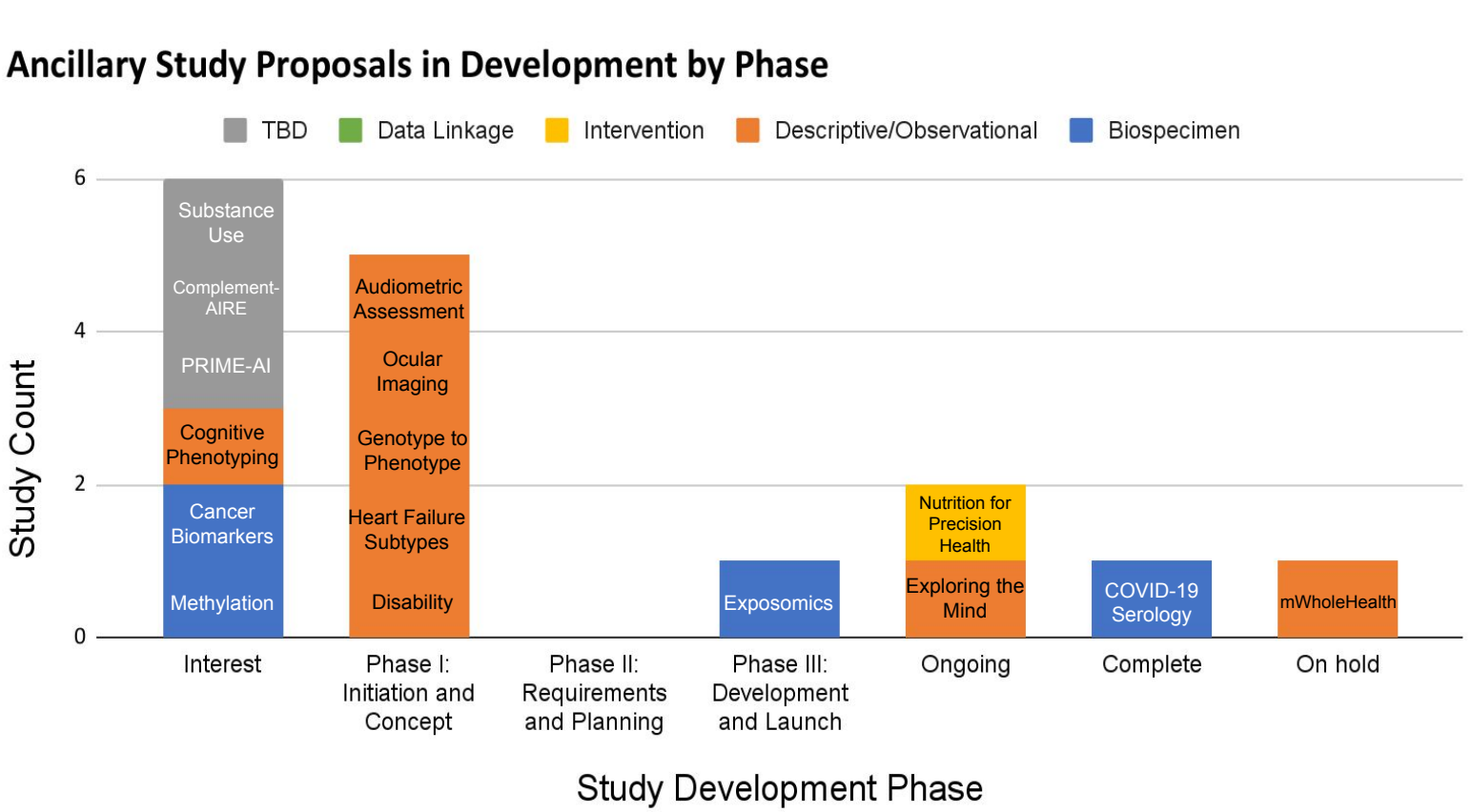
Core *All of Us* participant data
Broad Data use through the Researcher Workbench



This story + local promotion resulted in over 4,400 new consents in* All of Us *through that weekend!

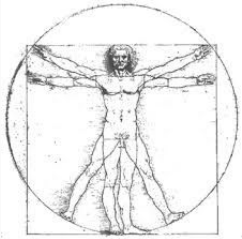
Watch the Video

Increasing interest in ancillary study opportunities across NIH Institutes, Centers, and Offices



Shifting Paradigm: Genotype to Phenotype Discovery

Phenotype



Genotype

All of Us RESEARCH PROGRAM

Large, diverse cohort
Clinical informatics

Targeted studies in Deep phenotyping
Utilize unique resource: the NIH Clinical Center

Evaluate loss of function variants with no association to disease to identify novel associations of genes and phenotypes

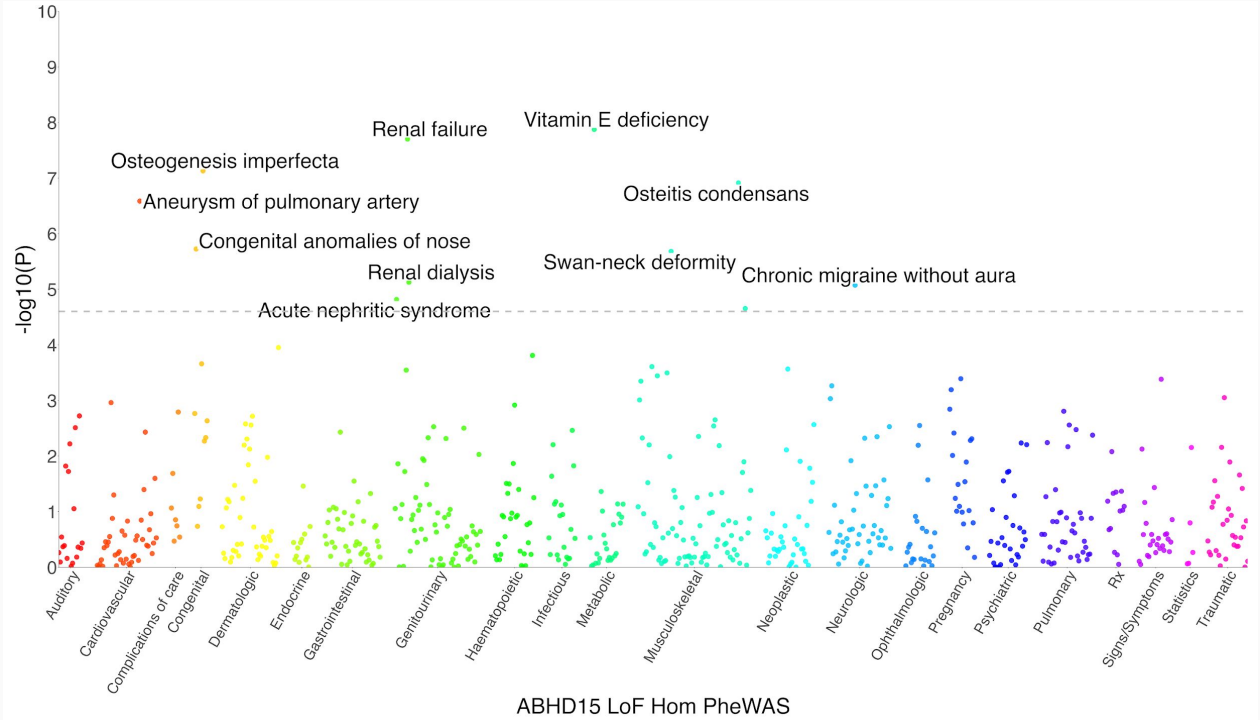
Reduce bias in ascertainment and increase diversity of research participation

Discover function of uncharacterized genes

Understand genetic disease resilience

Example: Phenotypes in *All of Us* associated with individuals homozygous for LOF in unknown gene *ABHD15*

- Reverse of a GWAS
- Genotyped cohort with coded EHR data
- Query is a variant or group of variants in a gene
- What phenotypes are associated?



Clinical Center can be used to confirm novel gene-phenotype associations via deep phenotyping

Resilience

nature biotechnology

ARTICLES

Analysis of 589,306 genomes identifies individuals resilient to severe Mendelian childhood diseases

Rong Chen[1,2,12], Lisong Shi[1,2,12], Jörg Hakenberg[1,2], Brian Naughton[3,11], Pamela Sklar[1,2,4], Jianguo Zhang[5], Hanlin Zhou[5], Lifeng Tian[6], Om Prakash[7], Mathieu Lemire[8], Patrick Sleiman[6], Wei-yi Cheng[1,2], Wanting Chen[5], Hardik Shah[1,2], Yulan Shen[5], Menachem Fromer[1,2,4], Larsson Omberg[9], Matthew A Deardorff[6], Elaine Zackai[6], Jason R Bobe[1,2], Elissa Levin[1,2], Thomas J Hudson[8], Leif Groop[7], Jun Wang[10], Hakon Hakonarson[6], Anne Wojcicki[3], George A Diaz[1,2], Lisa Edelmann[1,2], Eric E Schadt[1,2] & Stephen H Friend[1,2,9]

Genetic studies of human disease have traditionally focused on the detection of disease-causing mutations in afflicted individuals. Here we describe a complementary approach that seeks to identify healthy individuals resilient to highly penetrant forms of genetic childhood disorders. A comprehensive screen of 874 genes in 589,306 genomes led to the identification of 13 adults harboring mutations for 8 severe Mendelian conditions, with no reported clinical manifestation of the indicated disease. Our findings demonstrate the promise of broadening genetic studies to systematically search for well individuals who are buffering the effects of rare, highly penetrant, deleterious mutations. They also indicate that incomplete penetrance for Mendelian diseases is likely more common than previously believed. The identification of resilient individuals may provide a first step toward uncovering protective genetic variants that could help elucidate the mechanisms of Mendelian diseases and new therapeutic strategies.

NATURE BIOTECHNOLOGY VOLUME 34 NUMBER 5 MAY 2016

NIH Clinical Center - Opportunities with *All of Us*

- **Ancillary studies**
  - Deep phenotyping: undiagnosed genetic disorders <<>> associations with human phenotypes
    - Improve underdiagnosis of genetic disorders,
      - particularly in populations historically underrepresented in biomedical research
    - Identify unrecognized/latent phenotypes in individuals with pathogenic variants

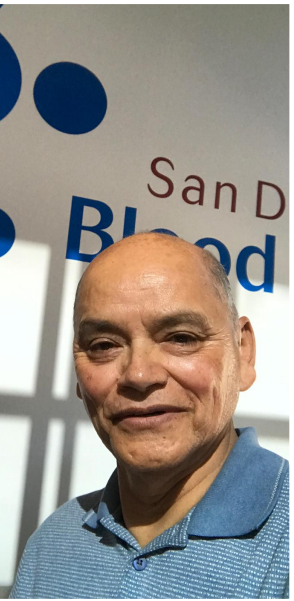
- **Co-enrollment with Clinical Center-led clinical trials/studies**
  - *All of Us* data to augment trials (SDOH, wearables, environmental exposures, etc.)
  - *All of Us* as a home for longitudinal trial data
  - Co-enrollment of clinical center patients in *All of Us*
    - Allows for sequencing, surveys and long term follow up for understanding the natural history of rare diseases

- ***All of Us* as a partner with the Clinical Center to NIH intramural research**
  - Training opportunities for early stage investigators
  - Share best practices on including the voice of the participant/patient
  - Developing return of results/value strategies

All of Us

Thank you!

@AllofUsResearch
@AllofUsCEO
#JoinAllofUs



Thank you to our 766,000+ participants!