The *All of Us* Research Program: Improving Health Through Diverse Technology, Huge Cohorts, and Precision Medicine





May 5, 2023

Joshua Denny, MD, MS
Chief Executive Officer

All of Us Research Program



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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 (GHD) emphasize the importance of this disease as a contemporary health hazard. Cardiovascular disease is now the lea."

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

now the lea nary heart d of all heart in the diag ment of CH decade, no bidity and curred. Thi slight increa which has b decades, wh been substan

Because c manifested a "silent" infa mortality in pital is still of best theraps preventive

Received for From the I Framingham, I tute, National Service, U. S. and Welfare, I Presented a The Americar 1961, Bal Har Requests fo Thomas R. Da tor, Heart Di green St., Fran

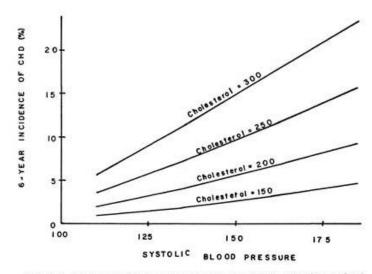


FIGURE 2. Six-year incidence of coronary heart disease according to level of systolic blood pressure at specified serum cholesterol levels (men 45 to 62 years). For explanation, see legends for Figure 1.

W CO

Framingham Heart Study

Enrolled 5,209 men and women in 1948

Some Framingham early discoveries:

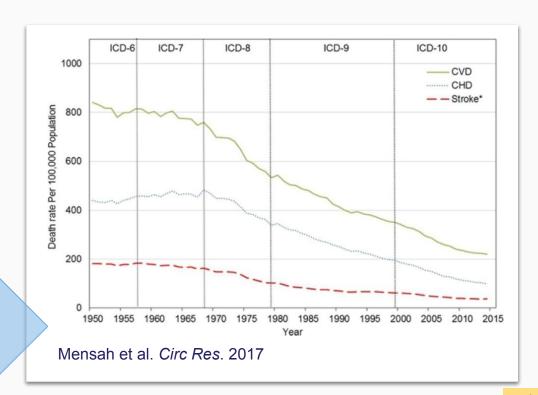
- 1960 Cigarettes increase heart disease
- 1961 cholesterol, blood pressure increase heart disease
- 1967 exercise decreases risk of heart disease; obesity increases it
- 1970 high blood pressure and atrial fibrillation cause stroke

The Strength of Large Cohort Studies

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

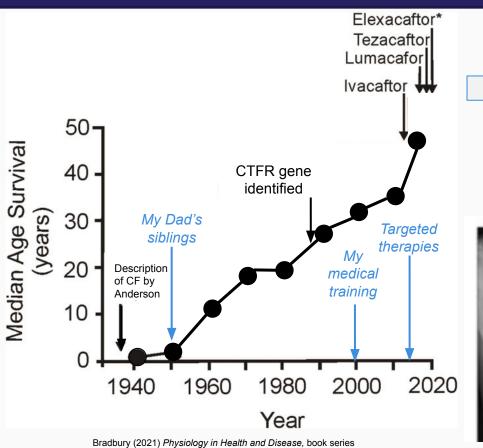
From 1950 - 1996: Heart disease mortality fell 56%, stroke rates fell by 70%

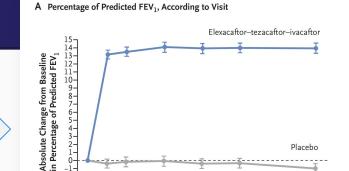
Since 1990, heart disease mortality has continued to fall by 22%



Could we have a similar experience with precision medicine in the next 40 years?

A Personal Story of Precision Medicine





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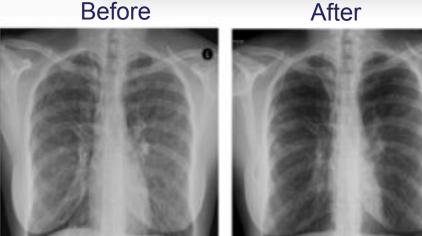
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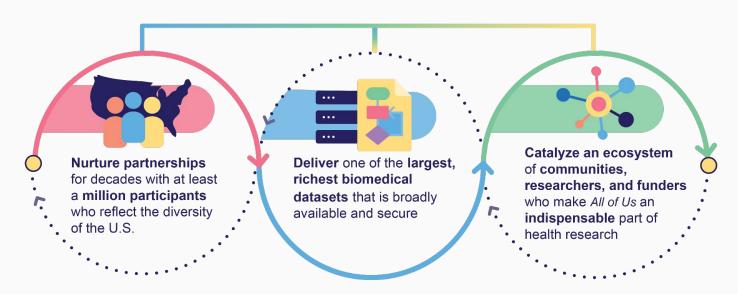


Base- Day Wk

line 15 4

The All of Us Research Program Mission

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



Made possible by a team that maintains a culture built around the program's core values

All of Us Research Program Core Values

Participation is open to all.

Participants reflect the rich diversity of the U.S.

Participants are partners.

Trust will be earned through transparency.

Participants have **access** to their information.

Data will be accessed **broadly** for research purposes.

Security and privacy will be of highest importance.

The program will be a catalyst for **positive change** in research.

Starting the Program Right by Engaging Participants

Community Engagement Studios in 2016

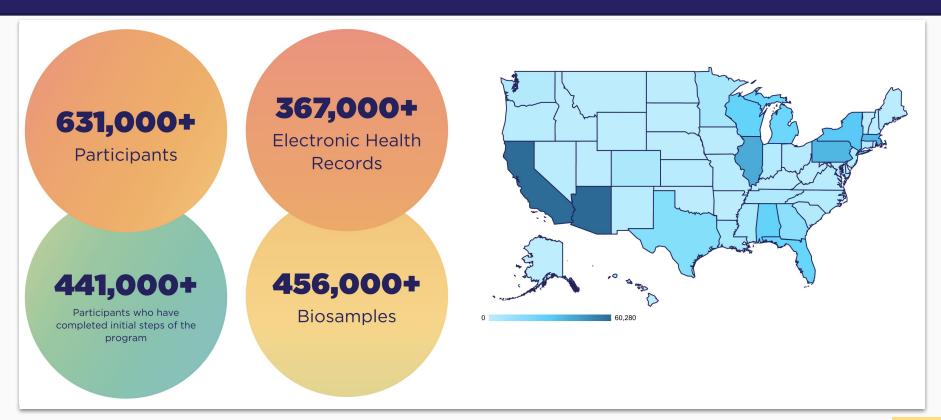




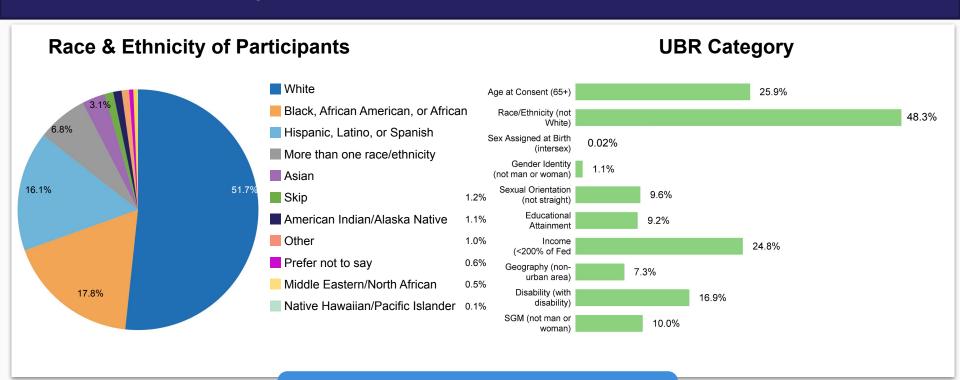
77 Studios in 17 cities with 654 community members

- 16 different demographic subgroups, 4 topics
- 46% racial and ethnic minorities
- 9% sexual and gender minorities

Enrolled 631K+ Participants With Continued Growth

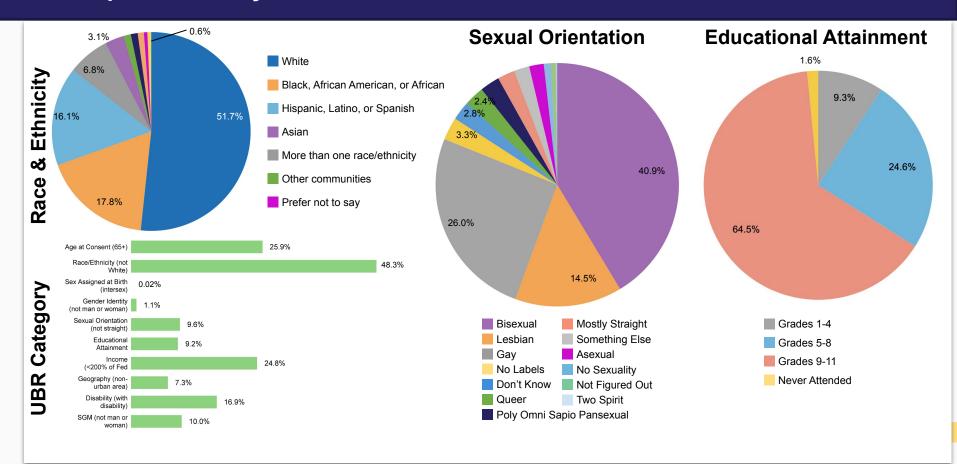


Participant Diversity



Over 80% of *All of Us* participants are underrepresented in biomedical research

Participant Diversity: Sexual and Gender Minorities (as of May 1, 2023)



All of Us Consortium Members (beyond community partners, as of April 2023)

The Participant Center









SunCoast



All of Us

New England



Quest



San Diego
Blood Bank

Spectrum

Health





· fitbit.

New York City

COLUMBIA

Weill Cornell

HEALTH+ HOSPITALS Harlem

→ NewYork-

¬ Presbyterian

Consortium







Communications & Engagement

LSA HEALTH

Medical Center

TUSKEGEE

LSU Health



All of Us Southern Network







HPO Network

(Health Care Provider

Organizations)











All of Us California































University of Arizona

and Banner Health



Trans America

Consortium

Henry Ford. Health System













BROAD









VA Medical Centers







Precision Health (NPH)



Illinois Precision

Blood & Tissue

Medicine Consortium



UI Health | ◎





Mass General Brigham

















LIGHT MEDICINE

MEDICAL CENTER

Tulane University

LIME HEERSINK



Nutrition for



























COLUMBIA







verilv

















All of Us Community and Provider Partner Network (as of April 2023)

























































For science For action For health























































Data Collected from All of Us Participants



Consent and Electronic Health Records



Participant Surveys



Physical Measurements

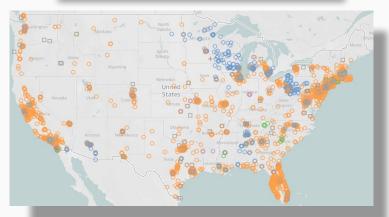


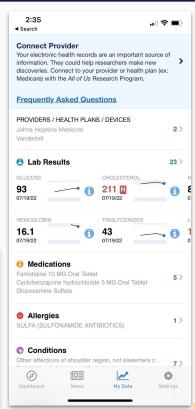
Biosamples



Mobile/Wearable Tech



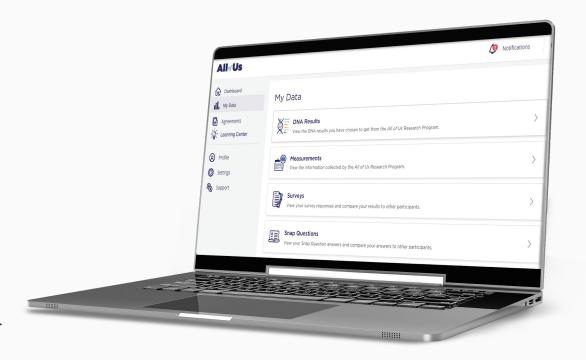




Returning Value for Participants

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



All of Us Genetics Return Strategy

Engagement

Health information

Genetic ancestry and traits results





7 regions (21 subregions) and 4 traits

- Sub-Saharan Africa
- Europe
- Oceania
- Southern Asia

- Eastern and northern Asia
- The Middle East and North Africa
- The Americas

- Ear wax
- Bitter taste perception
- Cilantro preference
- Lactose intolerance

Hereditary Disease Risk Report





59 genes (SNVs + indels)

- Breast cancer
- Ovarian cancer
- Uterine cancer
- Colorectal cancer
- Prostate cancer

- Melanoma
- Brain cancer
- Pancreatic cancer
- Stomach cancer

- Familial
 Hypercholesterolemia
- Cardiomyopathies
- Arrhythmias
- Arteriopathies

Medicine and your DNA Report



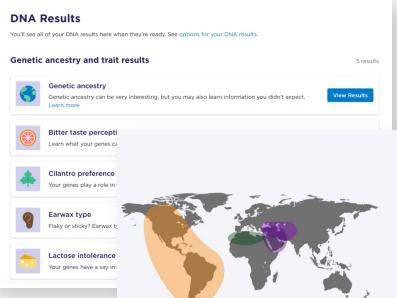
7 genes

- CYP2C19
- DPYD
- G6PD

- SLCO1B1
- NUDT15

- TPMT
- UGT1A1

Genetic Ancestry and Traits (as of May 1, 2023)





See Other Ancestry Groups Tested



182k+ participants were invited to receive their results



131k+ participants viewed their genetic ancestry results

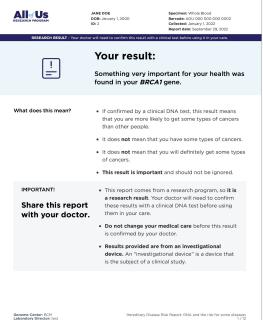


123k+ participants viewed genetic trait results

Genomic Health-Related Return of Results Now Released (as of May 1, 2023)

Hereditary Disease Risk

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



Medicine and Your DNA

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



>65,000 participants asked if they want health related results generated

19,066 participants viewed HDR results

19,206 participants viewed PGx results

All of Us is scaling to notify >200,000 participants!



Researcher Data Access

Data Curation

Raw Data Repository

Data
Harmonization
Privacy
Methodology
QA/QC

Individual Biospecimen and Participant Data (Available in the Future)

Controlled Tier

(Available Now)

No obvious PII. Genomics, real dates, eventually Clinical Narrative data, and more

Registered Tier

(Available Now)

Surveys, EHRs, Physical Measurements, shifted dates Exceeds HIPAA Safe Harbor Standards

Public Tier

(Available Now)

Summary Statistics Aggregate Counts



Future Ancillary Studies

Could recontact participants, use biospecimens, issue new surveys or DHT, enroll in clinical trials





All of Us Research Hub: Public Data Browser

Summary statistics of:

- EHR Data (Conditions, Drug Exposures, Lab & Measurements, Procedures)
- Genomic Variants
- Survey Questions (including COVID-19 surveys)
- Physical Measurements
- Open Access (no login required)

DataBrowser.ResearchAllofUs.org

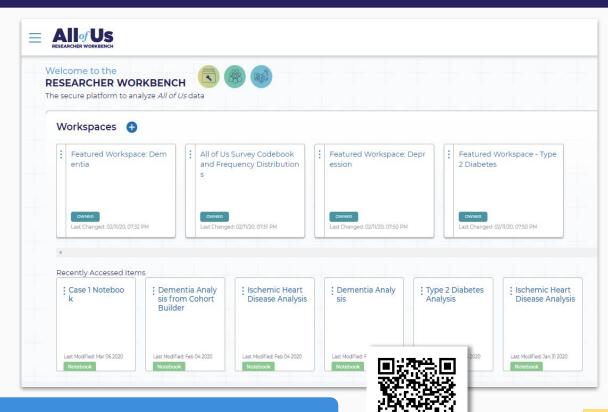




All of Us Researcher Workbench: Access to Row-Level Data for Analysis

Researcher Workbench

- Cloud-based central resource
- Passport access model just create, describe your workspace, and get to work! No separate IRB approval needed.
- Currently open to US nonprofits and nonprofit/for-profit academic and healthcare organizations
- Working to expand to international and broader for-profit audiences as we speak



ResearchAllofUs.org/Data-Tools/Workbench/

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

As of April 20, 2023, the *All of Us* Researcher Workbench contains the largest set 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

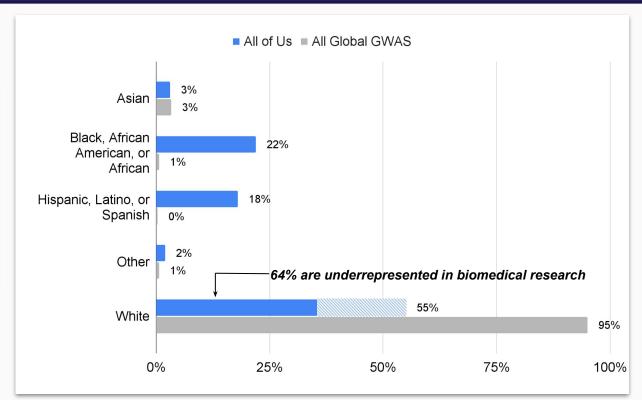


All of Us will Enhance Diversity of Genomic Studies

Updated genomic data set

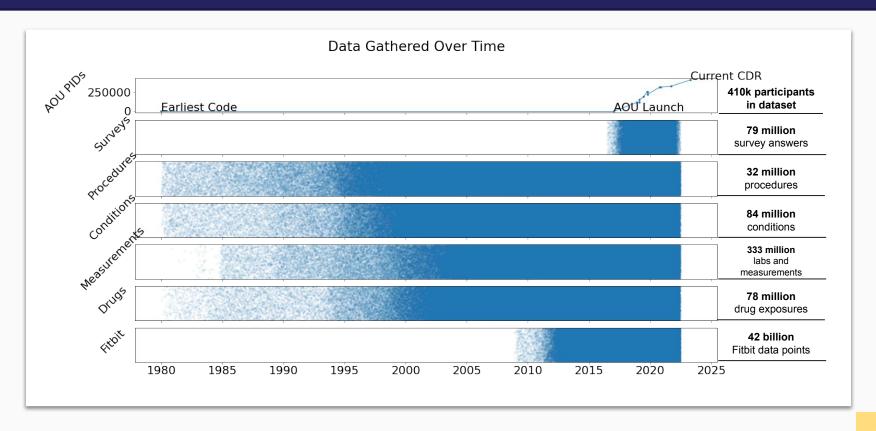
~50% diverse by race/ethnicity

77% underrepresented in biomedical research



All Global GWAS values from www.gwasdiversitymonitor.com. Values current as of April 20, 2023

Data on the Researcher Workbench is Diverse and Longitudinal

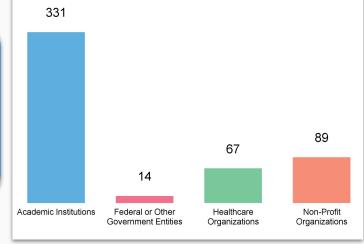


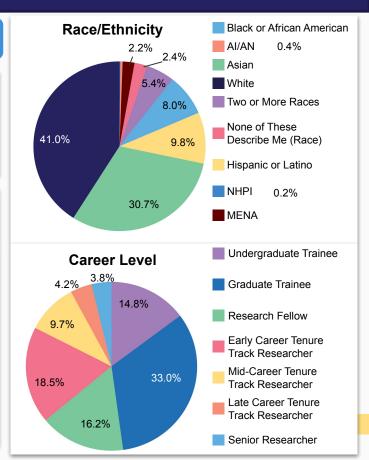
Researcher Workbench Usage and Diversity (as of May 1, 2023)





- 36 Historically Black Colleges & Universities
- 45 Hispanic Serving Institutions





Science Update (as of May 1, 2023)

All of Us Publications



152 Make us of All of Us Data



41 Published by the Program



researchallofus.org/publications/

nature > nature medicine > articles > article

Article | Open Access | Published: 10 October 2022

Association of step counts over time with the risk of chronic disease in the *All of Us* Research Program

Hiral Master, Jeffrey Annis, Shi Huang, Joshua A. Beckman, Francis Ratsimbazafy, Kayla Marginea Robert Carroll, Karthik Natarajan, Frank E. Harrell, Dan M. Roden, Paul Harris & Evan L. Brittain ⊠ Antibodies to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in *All of Us* Research Program Participants, 2 January to 18 March 2020

Keri N Althoff 🗷, David J Schlueter, Hoda Anton-Culver, James Cherry, Joshua C Denny, Isaac Thomsen, Elizabeth W Karlson, Fiona P Havers, Mine S Cicek, Stephen N Thibodeau

> Am J Hum Genet. 2023 Feb 2;110(2):228-239. doi: 10.1016/j.ajhg.2023.01.003. Epub 2023 Jan 20.

Functional interpretation, cataloging, and analysis of 1,341 glucose-6-phosphate dehydrogenase variants

phthalmology Glaucoma
Available online 15 March 2023
Press, Corrected Proof What's this?



Renee C Geck 1, Nicholas R Powell 2, Maitreya J Dunham 3

G OPEN ACCESS € PEER-REVIEWED



An Overview of Cancer in the First 315,000 All of Us Participants

Briseis Aschebrook-Killoy <u>B. Paul Zakin</u>, Andrew Craver, Sameep Shah, Muhammad G. Kibriya, Elizabeth Stepn Andrea Ramirez, Cheryl Clark, Elizabeth Cohn, Lucila Ohno-Machado, Mine Cicek, Eric Boerwinkle, Sheri D. Sch On behalf of the All of Us Research Program Investigators <u>BI</u> (view all]

Published: September 1, 2022 . https://doi.org/10.1371/journal.pone.0272522

Evaluating Discrepancies in Self-Reported
Glaucoma and Electronic Health Records in
the National Institutes of Health All of Us
Database

Health disparities in the treatment of bipolar disorder

Vladimir Tchikrizov^a, Mark E. Ladner^a, Felicia V. Caples^b, Mitzi Morris^c, Christina D. Jordan^c, Joyce E. Balls-Berry^d, Monica J. Taylor-Desir^e, Mark J. Vallender^{a,*} Published in final edited form as: Ophthalmol Sci. 2022 March; 2(1): . doi:10.1016/j.xops.2021.100099.

Novel Association between Opioid Use and Increased Risk of Retinal Vein Occlusion Using the National Institutes of Health *All* of Us Research Program

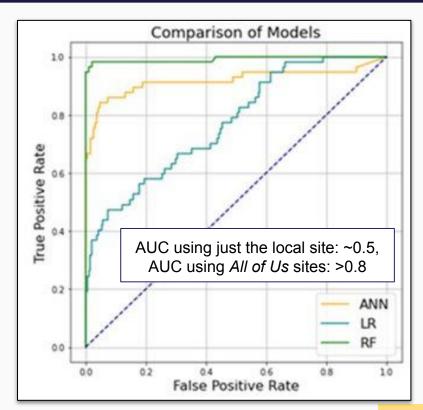
Machine Learning in All of Us to Predict Glaucoma Outcomes

Predictive Analytics for Glaucoma Using Data From the All of Us Research Program



SALLY L. BAXTER, BHARANIDHARAN RADHA SASEENDRAKUMAR, PAULINA PAUL, JIHOON KIM, LUCA BONOMI, TSUNG-TING KUO, ROXANA LOPERENA, FRANCIS RATSIMBAZAFY, ERIC BOERWINKLE, MINE CICEK, CHERYL R. CLARK, ELIZABETH COHN, KELLY GEBO, KELSEY MAYO, STEPHEN MOCKRIN, SHERI D. SCHULLY, ANDREA RAMIREZ, AND LUCILA OHNO-MACHADO, ON BEHALF OF THE ALL OF US RESEARCH PROGRAM INVESTIGATORS

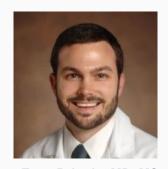
Conclusion: Models trained with national *All of Us* data achieved **superior performance** compared to using single-center data.



All of Us Discoveries: Physical Activity and Human Disease



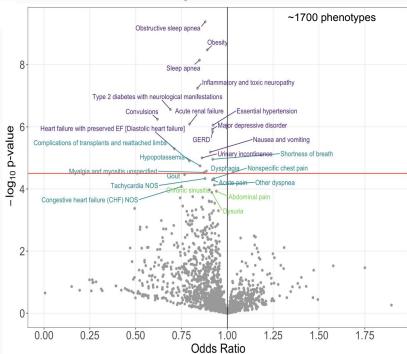
Hiral Master, PT, PhD, MPH, CPH
Senior Scientist at
Vanderbilt University Medical Center



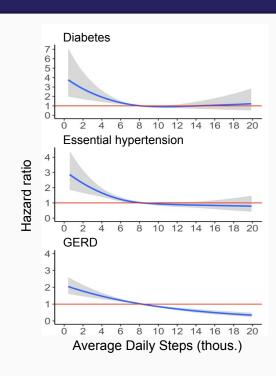
Evan Brittain, MD, MSc

Associate Professor of Medicine, Division of
Cardiovascular Medicine at
Vanderbilt Translational and Clinical
Cardiovascular Research Center

Incident Diagnoses after 6 months

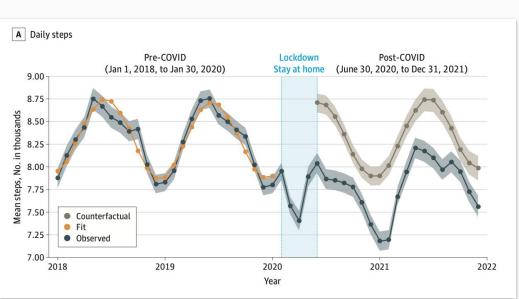


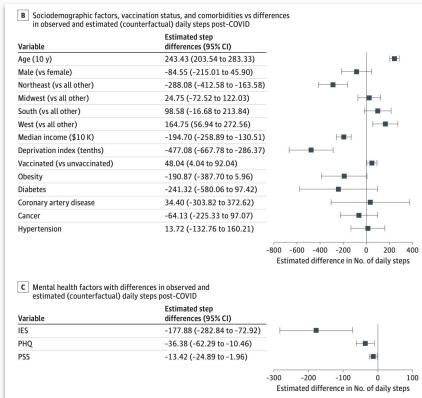
- Analysis uses average of daily steps prior to diagnosis.
- Effect size per 1000 steps, adjusted for age, sex, race



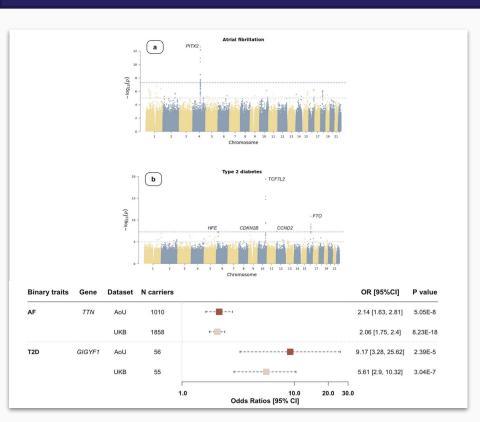
Adjusted for age, sex, race, CAD, cancer, BMI, systolic blood pressure, education level, smoking, alcohol use, and monthly daily steps (time varying)

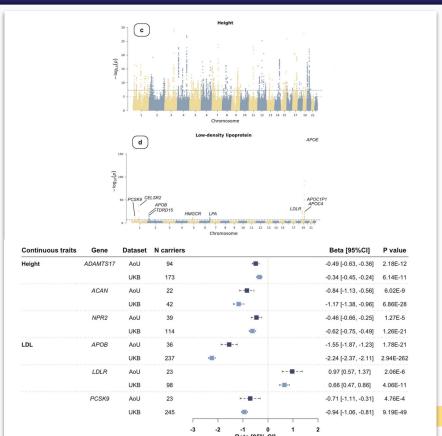
Impact of the COVID-19 Pandemic, Sociodemographics, and Mental Health Factors on Average Daily Steps



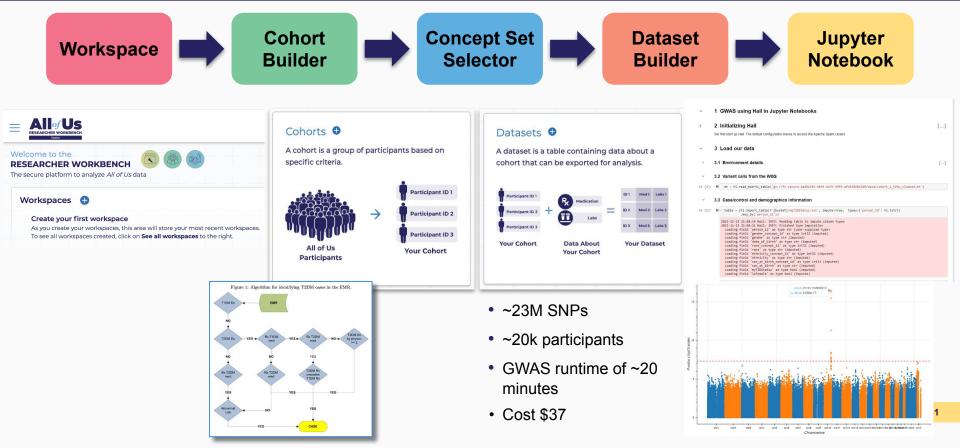


Common and Rare Variants Associated with Cardiometabolic Traits in *All of Us* Participants





What Does It Look Like To Do an Analysis in *All of Us*? A Genome Wide Association Study (GWAS) of Type 2 Diabetes



All of Us Data Includes Range of Diseases

Conditions	Domain	Participants
Heart Disease	Heart	73,100
Obesity	Endocrine	65,740
Type 1 Diabetes	Endocrine	5,620
Type 2 Diabetes	Endocrine	45,360
Any cancer	Cancer	42,080
Asthma	Pulmonary	40,560
Chronic Obstructive Pulmonary Disorder	Pulmonary	19,740
Epilepsy	Neuro	7,440
Stroke	Neuro	640
Rheumatoid Arthritis	Autoimmune	6,980
Osteoarthritis	Autoimmune	81,980

Conditions	Domain	Participants
Depressive Disorder	Mental Health	67,380
Bipolar Disorder	Mental Health	12,820
Dementia	Mental Health	4,760
Human Immunodeficiency Virus	Infectious Disease	4,640
COVID-19*	Infectious Disease	58,000*
Alcohol Abuse (AUDIT-C)	Abuse	84,000
Opioid Usage	Medication	155,000
Age-Related Macular Degeneration	Eye	4,740
Hearing loss	Hearing	30,400
Falls	Aging/Nursing	4,860

^{*}using combination of diagnosis code, lab test, and COVID survey answers

All of Us Researcher Workbench: Access to Row-Level Data for Analysis



LEARN MORE ABOUT THE DATA AVAILABLE

Explore the data available through the <u>Data Browser</u>, which provides interactive views of aggregate-level participant data. Learn about individual-level <u>data access tiers</u> and the <u>Researcher Workbench tools</u>.



CHECK FOR YOUR INSTITUTION'S AGREEMENT

Before you can register, your institution must have a <u>Data Use</u> and <u>Registration Agreement</u> in place with *All of Us* to ensure data security.



CREATE A RESEARCHER WORKBENCH ACCOUNT

Complete your researcher profile, sign the Terms of Service, and agree to the Privacy Policy.



VERIFY YOUR IDENTITY USING LOGIN.GOV

Verify your identity using Login.gov. You may need to provide an SSN and a state-issued ID. Your institution may also require you to use an eRA Commons account. If so, contact your institution directly. Read more about Login.gov.



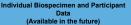
COMPLETE ALL OF US RESEARCH TRAINING

The mandatory training provides education on conducting responsible and ethical research with data from *All of Us* participants. Please allow at least one hour to complete.



SIGN THE DATA USER CODE OF CONDUCT

The Data User Code of Conduct is an agreement that outlines the program's expectations for researchers.



Controlled Tier (Available Now) obvious PII. <u>Genomics,</u> real dates, eventu Clinical Narrative data, and more

Registered Tier
(Available Now)
Surveys, EHRs, Physical Measurements
Exceeds HIPAA Safe Harbor Standards

Public Tier (Available Now) Summary Statistics Aggregate Counts



ResearchAllofUs.org/Data-Tools/ Workbench/

What Kind of Research Can All of Us Support?

Example studies in All of Us

- Associations between diseases, medications, behaviors, SDOH, genomics
- Health disparities
- Historically underrepresented populations
- Genomics and PGx
- Drug target discovery
- Early disease detection
- Geospatial linkages (future)
- Insert your topic here

Modalities of research All of Us supports

- AI/ML
- Risk stratification
- Predictive analytics
- Phenotype algorithms & cohort development
- Novel method development
- Basic EHR investigations
- Validation of other studies

All of Us is not

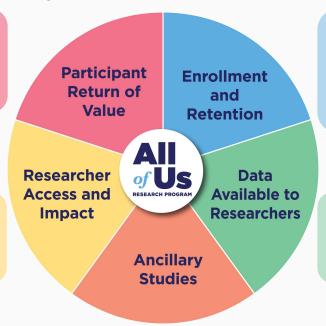
- A representative US sample
- A study with uniform follow-up of all variables

Our Five Year Goals (2021 - 2026)

Incorporate participant **return of value** into data collections and assess its impact, including return of information to participants on **genomics** and **EHR**.

Establish a diverse global community of 10,000 researchers productively using *All of Us* data.

By end of 2026, we will:



Launch **ancillary studies** as a core and scalable capability, expanding the cohort and delivering phenotypic, lifestyle, environmental, and biologic data.

Enroll 1 million participants who reflect the diversity of the U.S., cover the lifespan, and have shared all baseline elements. Of these participants, 500,000 participate in ongoing data donation opportunities.

Expand data available for 1 million participants to include survey, health data streams, a whole genome sequence, environmental data, and physical measures.

Nutrition for Precision Health

Powered by the All of Us Research Program





Examine baseline diet and physiological responses to meal challenges

10,000 All of Us participants



Examine responses to 3 short-term intervention diets in free-living controlled feeding studies

1,500-2,000 Module 1 participants



Examine responses to 3 short-term intervention diets in domiciled controlled feeding studies

500-1,000 Module 1 participants

In all 3 modules

- Collect microbiome, physiological, metabolic, behavioral, cognitive, and environmental data, and leverage
 existing genomic, EHR, and survey data, and conduct mixed meal challenges to model the impact of diet and
 dietary patterns on physiological responses
- Use machine learning and artificial intelligence to develop predictive algorithms

Funding Opportunities with All of Us



OTA-22-006:

ROA for All of Us Engagement, Communications, and Enrollment Partnerships

Submission Due Dates: Multiple, final on May 23, 2025



RFA-HG-21-041:

R01 Clinical Trial Optional for New Investigators to Promote Workforce Diversity in Genomics, Bioinformatics, or Bioengineering and Biomedical Imaging Research

Submission Due Date: February 22, 2024, 5:00 PM Applicant's time zone

Coming soon: Two 10-min mental health and well-being surveys

Emotional Health History and Well-Being

Emotional Health History and Well-Being

12 minutes

Start



Generalized and lifetime anxiety
Present and past depression
Suicidal behavior
Childhood and adult adversity/trauma
General well-being

Behavioral Health and Personality

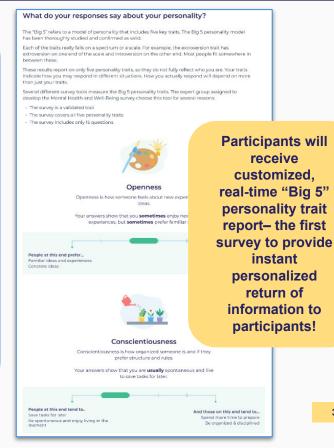
Behavioral Health and Personality

10 minutes

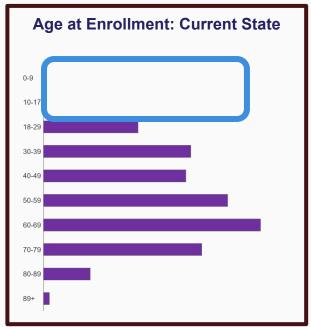
Start

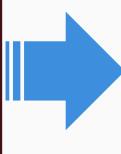


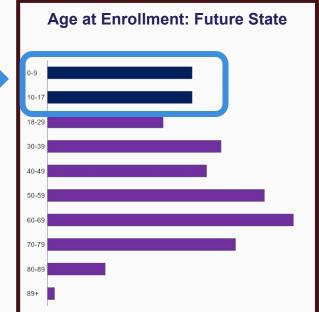
Adult ADHD
Bipolar disorder
Psychosis
Panic disorder
Obsessive compulsive disorder
Social phobia and agoraphobia
Personality



Launching our Pediatric Cohort









Sara Van Driest, MD, PhD
Director of Pediatrics, All of Us
Previously, Assoc Prof of
Pediatrics and Clinical
Pharmacology, VUMC



SanD













@AllofUsResearch @AllofUsCEO #JoinAllofUs









Thank you to our 631,000+ participants!