January 17, 2020
Precision Medicine and Pharmacogenomics: Propelling Practice and Proof in Populations

All of Us RESEARCH PROGRAM

Creating a Research Program for All of Us

#JoinAllofUs

NIH National Institutes of Health

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Professor of Surgery, Contact Principal Investigator
University of Arizona Health Sciences

Disclosures

- Research funding: The University of Arizona-Banner Health *All of Us* Research Program is funded by NIH Award OT2OD026549.

- Conflicts of Interest: None.

Goals

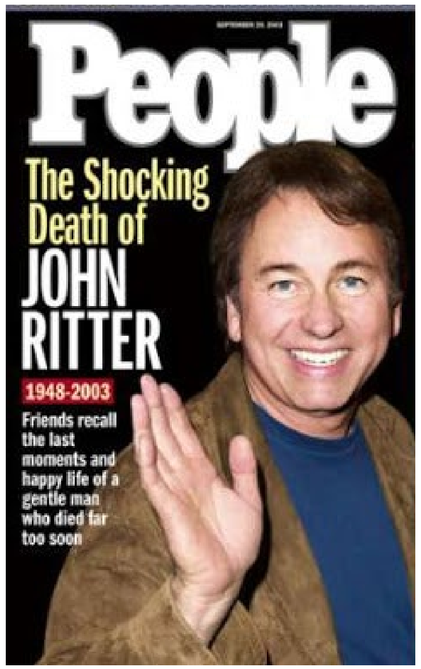
- Understand the **mission, objectives, and scientific framework** of the *All of Us* Research Program

- **Discuss the unique resource** currently being developed within the *All of Us* Research Program

- Be able to **identify clinical and research questions** where *All of Us* could serve as a data source

Aortic Dissection

- Aortic aneurysms and dissection were the primary cause of 17,215 deaths in 2009 according to data from the Center for Disease Control and Prevention.
- About 20% of patients with aortic dissection die before reaching the hospital.
- Certain genetic syndromes of connective tissue increase risk for fatal aortic dissection: Marfan syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, and Turner syndrome.



Rohan Bhandari & Yogendra Kanthi. May 2, 2018. The Genetics of Aortic Aneurysms. American College of Cardiology. https://www.acc.org/latest-in-cardiology/articles/2018/05/02/12/52/the-genetics-of-aortic-aneurysms

Challenges in Genetic Analysis of Bicuspid Aortic Valve Aortopathy

- Genetics multifaceted: primary genetic mutations, epigenetics, and environmental influences
- BAV has been observed in other genetic conditions such as DiGeorge syndrome, Loeys-Dietz syndrome and Shone's complex, making it even more complicated to tease out the exact genetic cause(s)
- GWAS studies have identified some candidate genes; however, pinpointing specific gene associations requires more high-powered studies across diverse populations

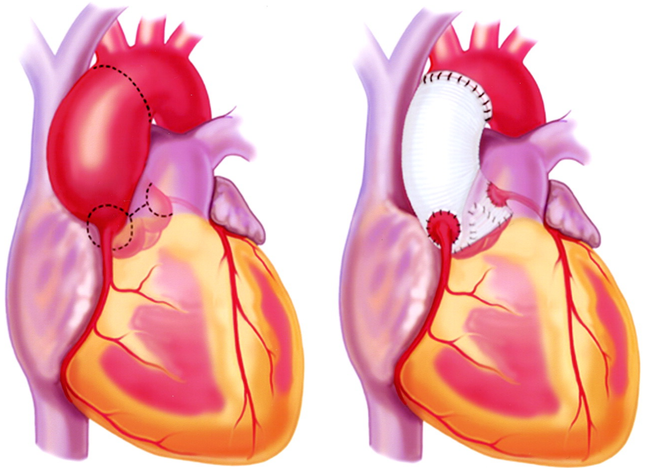
Table 1. Gene mutations associated with bicuspid aortic valve in human studies

Gene	Function	Genetic defect and clinical phenotype	References
NOTCH1	Transmembrane receptor	Gene mutations in isolated and familial BAV; LVOT defects	[32–38]
ACTA2	Contractile protein	Gene mutation in BAV with familial thoracic aortic aneurysm	[46]
TGF-β2	Signaling pathway	Gene mutation in BAV with familial aortic aneurysm	[43]
FNB1	Matrix protein	Gene mutations in isolated BAV; BAV with Marfan syndrome	[34,48]
KCNJ2	Potassium channel	BAV in Andersen syndrome	[47]
GATA5	Transcription factor	Rare variants in nonsyndromic BAV; BAV with aortic coarctation	[50,51]
Nkx2-5	Transcription factor	Gene mutation in familial BAV	[49]
SMAD6	Signaling pathway	Rare variants in BAV with mild aortic stenosis and aortic coarctation	[52]

BAV, bicuspid aortic valve; LVOT, left ventricular outflow tract.

Andreassi & Della Corte, *Current Opinion Cardiology,* 2016;31,6:586-592

Aortic aneurysm graft repair



Isselbacher, *Circulation,* 2005;111:816-828

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BRCA1 and *BRCA2* Genes

- Discovered in 1994, about 72% of women who inherit *BRCA1* mutation, and about 69% of women who inherit *BRCA2* mutation, will develop **breast cancer** by the age of 80.
- About 44% of women with *BRCA1* mutation and about 17% of women with *BRCA2* mutation will develop **ovarian cancer** by the age of 80.
- Women can use the results of genetic tests to make informed decisions — such as whether to surgically remove the breasts (preventive mastectomy) or ovaries (preventive oophorectomy) — to reduce their cancer risk.

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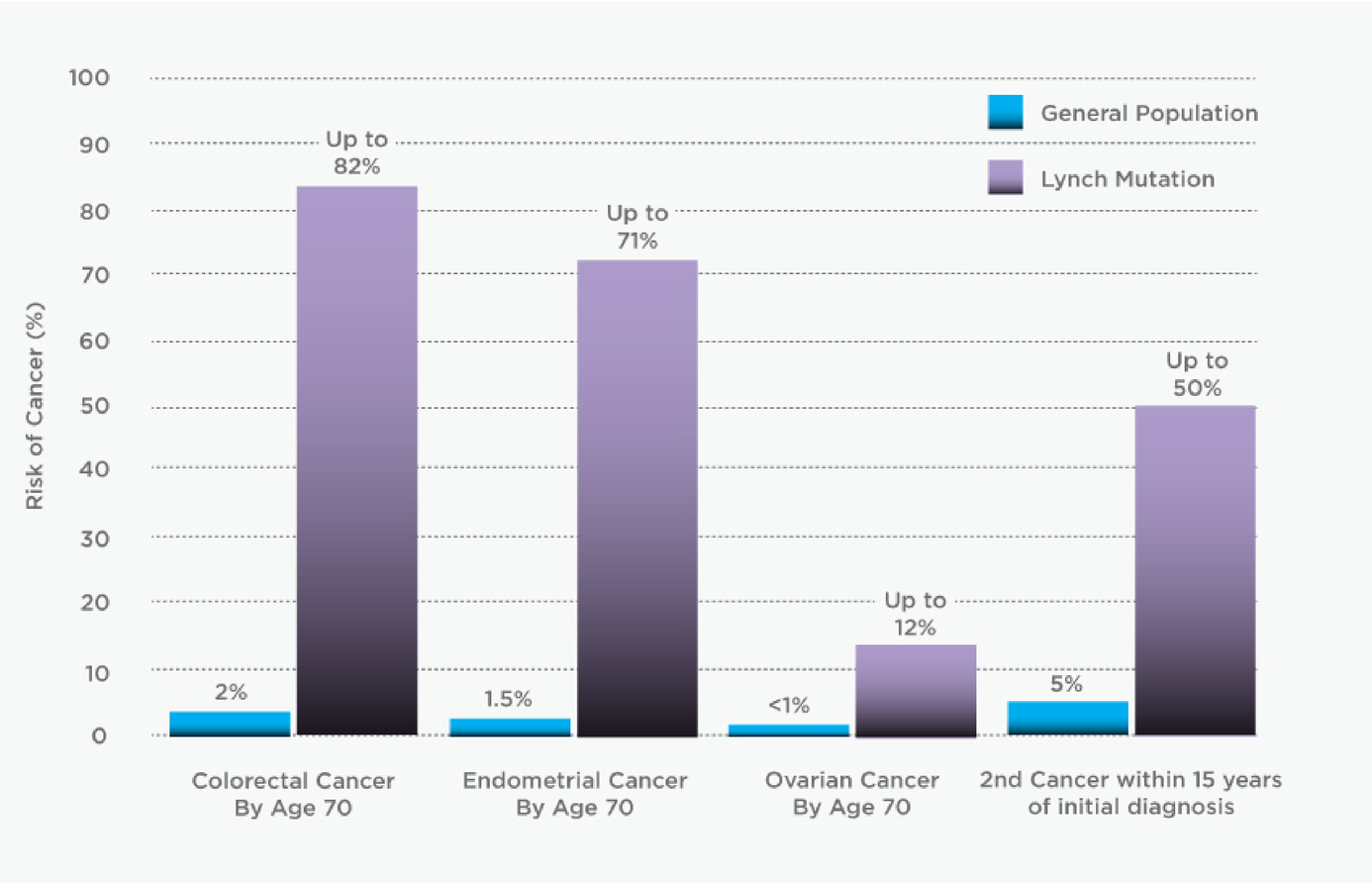
JAMA. 2017 Jun 20;317(23):2402-2416. doi: 10.1001/jama.2017.7112. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. Kuchenbaecker KB et al. https://www.ncbi.nlm.nih.gov/pubmed/28632866

Lynch Syndrome and Risk of Inherited Cancer

- One of the most common causes of inherited colon cancer
- Autosomal dominant heritability pattern; caused by mutations in one of five genes (MLH1, MSH2, MSH6, PMS2, EPCAM)
- 80% chance of colon cancer
  - In women, 40-60% chance of uterine cancer, 10-12% chance of ovarian cancer
- Monitoring of affected individuals should begin in early 20s (colonoscopy every year, uterine biopsy, upper endoscopy); if cancer is detected, complete removal of the affected organ is necessary



Hereditary Colon Cancer. https://myriad.com/patients-families/disease-info/colon-cancer/

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Cystic Fibrosis

- **1989**: Dr. Francis Collins & lab discover the first genetic mutation for cystic fibrosis (CF)
- **2019**: FDA approves treatment for 90% of patients with CF, many of whom had no approved therapeutic options

Left: Jenny, Age 8, Diary Entry

Right: Jenny, Age 38, with Daughter

More work remains to be done to help the 10% of CF patients for whom current drugs still don't work:

"Beyond that, wouldn't it be great if biomedical science could figure out a way to permanently cure CF, perhaps using nonheritable gene editing, so no one needs to take drugs at all? It's a bold dream, but look how far a little dreaming, plus a lot of hard work, has taken us so far in Jenny's life…"

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Francis Collins. October 2019. Dare to Dream: The Long Road to Targeted Therapies for Cystic Fibrosis. NIH Director's Blog. https://directorsblog.nih.gov/2019/10/31/dare-to-dream-the-long-road-to-targeted-therapies-for-cystic-fibrosis/

A Vision Spanning Three Decades

"*All of Us* is among the most ambitious research efforts that our nation has undertaken."

NIH Director Francis Collins, M.D., Ph.D.

Mission & Objectives

Mission:

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

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

Deliver the largest, richest biomedical dataset ever, making it as easy, safe, and free to use as possible

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

The *All of Us* Research Program: An Innovative Research Effort

- **Diversity at the scale of 1 million people or more**
- **Focus on participants as partners**
- **Longitudinal design, ability to recontact**
- **Multiple data types:** EHR, surveys, baseline physical measurements, biospecimens, genomics
- **National, open resource for all:** broadly accessible to all researchers with open source software & tools
- **Security and privacy safeguards**

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Current Protocol

Enroll, Consent and Authorize EHR

- Recruiting 18+ years old initially; plan to include children in future
- Online, interactive consent
- Includes authorization to share Electronic Health Record (EHR) data

Answering Surveys

- Initial surveys: The Basics, Overall Health, Lifestyle, Health Care Access & Utilization, Family Medical History, Personal Health History
- Additional surveys will be released on an ongoing basis.

Physical Measurements*

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

*Based on diverse sampling and capacity

Provide Biosamples*

- Blood (or saliva, if blood draw is unsuccessful) for DNA, plasma, serum, cfDNA, RNA
- Urine specimen
- Biosamples will be stored at the program's biobank

*Based on diverse sampling and capacity

Wearables and Digital Apps

- Share data from wearable fitness devices, starting with Fitbit
- More integrations to come, e.g., integrated apps to track mood & cardio-respiratory fitness

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Electronic Health Records

- Participants are asked to authorize linkage of their EHR information.
- Initial data types:
  - Demographics
  - Visits
  - Diagnoses
  - Procedures
  - Medications
  - Laboratory visits
  - Vital signs
- Expanded data types to come

All of Us Consortium Members

The Participant Center

Scripps Research Translational Institute · BlueCross BlueShield · Community Blood Center of the Carolinas · DXC.technology · EMSI HEALTH · Montage Marketing · National Blood Collaborative · patientslikeme · Qualcomm · Quest Diagnostics · QTC A Leidos Company · Sage Bionetworks · San Diego Blood Bank · Walgreens · WebMD

Communications & Engagement

WONDROS · The University of Utah · HCM Strategists

HPO Network

(Health Care Provider Organizations)

RMCs

All of Us California

UC San Diego Health · UCI Health · UCSF University of California San Francisco · UC DAVIS HEALTH · Cedars-Sinai · USC University of Southern California · San Diego Blood Bank · ECRMC El Centro Regional Medical Center

Illinois Precision Medicine Consortium

Northwestern Medicine · The University of Chicago · NorthShore University HealthSystem · RUSH · Cook County Health · The University of Illinois College of Medicine · UI Health

All of Us New England

Brigham Health: Brigham and Women's Hospital · Brigham and Women's Faulkner Hospital · Massachusetts General Hospital · Newton-Wellesley Hospital · McLean Hospital · Partners HealthCare · Boston Medical

Trans America Consortium

Henry Ford Health System · Essentia Health · BaylorScott&White Health · Spectrum Health · Reliant Medical Group Part of OptumCare

New York City Consortium

Columbia University Medical Center · NYC Health+ Hospitals · NewYork-Presbyterian · Weill Cornell Medicine

All of Us Southern Network

UAB School of Medicine: The University of Alabama at Birmingham; Selma Family Medicine · UAB School of Medicine: The University of Alabama at Birmingham; Montgomery Regional Medical Campus · The University of Mississippi Medical Center · UAB Medicine · Tulane University · LSU Health New Orleans · UAB School of Medicine: The University of Alabama at Birmingham; Huntsville Regional Medical Campus · The University of Alabama University Medical Center · USA Health · Cooper Green Mercy Health Services

All of Us SouthEast Enrollment Center

University of Miami Miller School of Medicine · Emory University · Morehouse School of Medicine · University of Florida

All of Us Wisconsin

Marshfield Clinic Health System · Wisconsin: University of Wisconsin-Madison · Froedtert & Medical College of Wisconsin

All of Us Pennsylvania

University of Pittsburgh · Temple University

University of Arizona and Banner Health

The University of Arizona · Banner Health

FQHCs (Federally Qualified Health Centers)

Cherokee Health Systems · Jackson-Hinds Comprehensive Health Center · San Ysidro Health · Community Health Center, Inc. · Eau Claire · HRHCare Community Health

VA Medical Centers

VA | U.S. Department of Veterans Affairs

Participant Technology Systems Center (PTSC)

vibrent

Biobank

Mayo Clinic

Data & Research Center (DRC)

Vanderbilt University Medical Center · Broad Institute · verily · Columbia University Medical Center · School of Public Health University of Michigan · Northwestern Medicine · UTHealth The University of Texas Health Science Center at Houston

Genomics Partners

Baylor College of Medicine · Johns Hopkins Medicine · UTHealth The University of Texas Health Science Center at Houston · HudsonAlpha Institute for Biotechnology · Broad Institute · color · Partners HealthCare · University of Washington

All of Us Research Program

Genomics Plans

- **Infrastructure**
  - **Three Genome Centers**: to generate genotyping & whole genome sequencing for 1M participants
  - **Genetic Counseling Resource**: to support the responsible return of information to interested participants

- **Return of Information**

  Over time, the program anticipates providing several kinds of information of interest to participants:
  - Common traits
  - Ancestry
  - Genetic findings connected with risk of certain diseases
  - Pharmacogenomic information

HGSC HUMAN GENOME SEQUENCING CENTER

CIDR Center for Inherited Disease Research Johns Hopkins University

UTHealth The University of Texas Health Science Center at Houston

BROAD INSTITUTE

PARTNERS HEALTHCARE

color

Genome Sciences UNIVERSITY OF WASHINGTON

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Scientific Framework

Scientific Framework

Enable research that will:

- Increase wellness and resilience, and promote healthy living
- Reduce health disparities and improve health equity in populations that are historically underrepresented in biomedical research (UBR)
- Develop improved risk assessment and prevention strategies to preempt disease
- Provide earlier and more accurate diagnosis to decrease illness burden
- Improve health outcomes and reduce disease impact through improved treatment and development of precision interventions

National Progress

- Opened our doors nationally on May 6, 2018
- >245k participants have completed the full protocol, from all 50 states
  - >81% are underrepresented in biomedical research;
  - >52% are racial/ethnic minorities
- Built significant infrastructure to support the program:
  - 100+ academic, VA, FQHC, technology, & community partners
  - Bilingual enrollment website, participant portal, app, and call center
  - Biobank and 24-hour shipping process with capacity for 35M+ vials
  - Interactive mobile exhibits that travel the country

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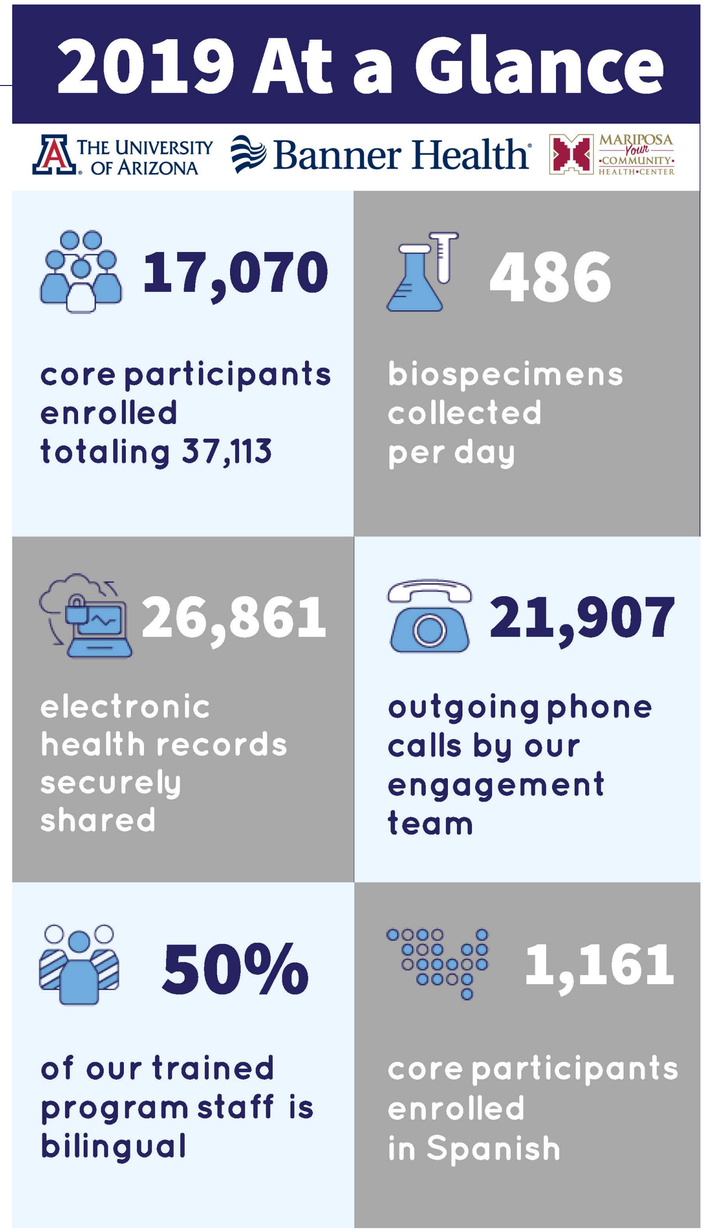
UArizona's Progress

- >37,000 participants have completed the full protocol from the University of Arizona-Banner Health award
  - >82% are underrepresented in biomedical research;
  - >53% are racial/ethnic minorities
- Among our dedicated research team:
  - 486 biospecimens collected per day
  - 26,861 EHR records securely shared
- Actively enrolling across 14 medical centers:
  - 8 enrollment sites in Central AZ
  - 5 enrollment sites in Southern AZ
  - 1 enrollment site in Northern Colorado
  - 2 mobile health units in partnership with MEZCOPH



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Research Hub

Banner Health | The University of Arizona

All of Us RESEARCH PROGRAM

RESEARCHER WORKSHOP

Jan. 28 from 9am - 3pm

Register now! http://bit.ly/AllofUsResearch

- Introducing the Researcher Workbench, a new resource that will house data from the program that will be available to researchers
- Learn types of data the program collects, what tools are needed to analyze the data, and how researchers will be able to access the data
- Hear from UArizona colleagues who are conducting “proof of concept” demonstration projects

Special Guest:
Andrea H. Ramirez, M.D.

Investigator, All of Us Data & Research Center
Assistant Professor of Medicine, Vanderbilt University

Health Sciences Innovation Building

1670 E Drachman St, Tucson, AZ 85721

Forum & Room 306

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Research Hub Website

- Visit ResearchAllofUs.org
- Goal: To provide more information around program data and tools
  - **Data Snapshots**: broad cohort metrics
  - **Data Browser**: interactive tool
  - **Survey Explorer**: source information

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Selected Data Snapshots

(Updated 1/12/20)

Participants at a Glance

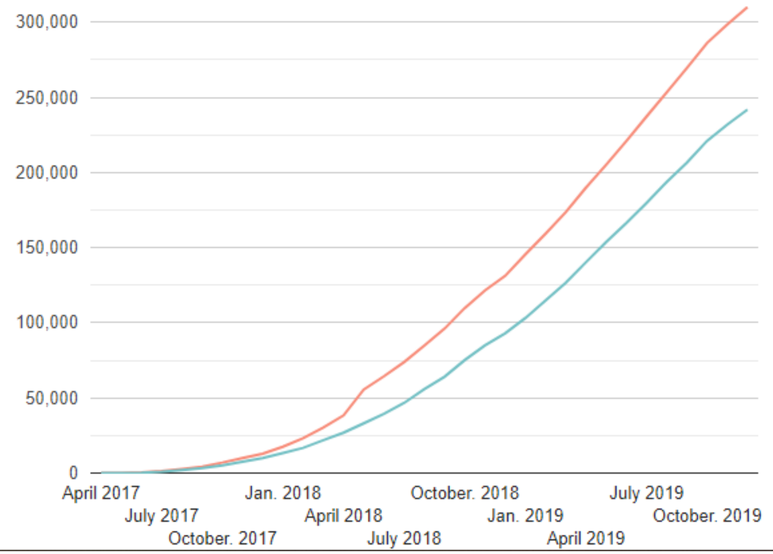
314,000+
Participants

245,000+
Participants who have completed initial steps of the program

Enrollment Numbers

This graph represents participants (individuals who have consented to join the program) and participants who have completed all initial steps of the program (i.e., those who have consented, agreed to share their electronic health records, completed the first three surveys, provided physical measurements, and donated at least one biospecimen stored at the biobank).

The following numbers are approximated to protect participants' privacy. Numbers are updated as of January 12, 2020.



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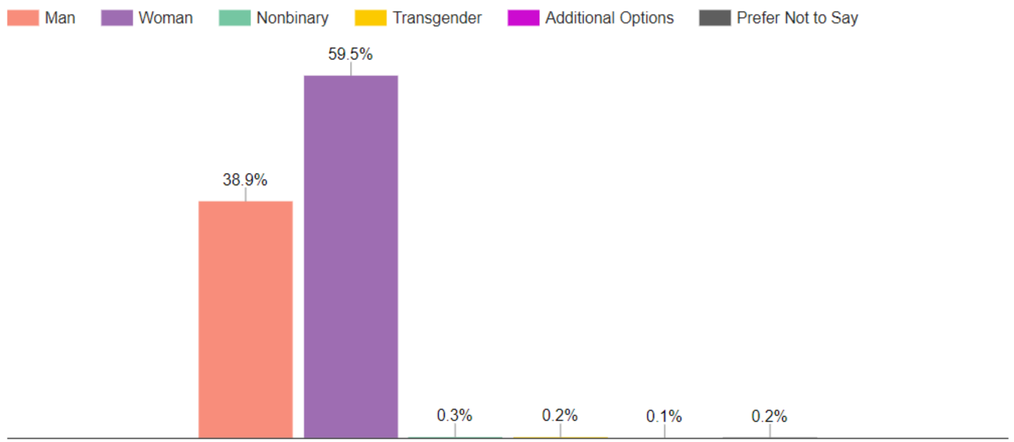
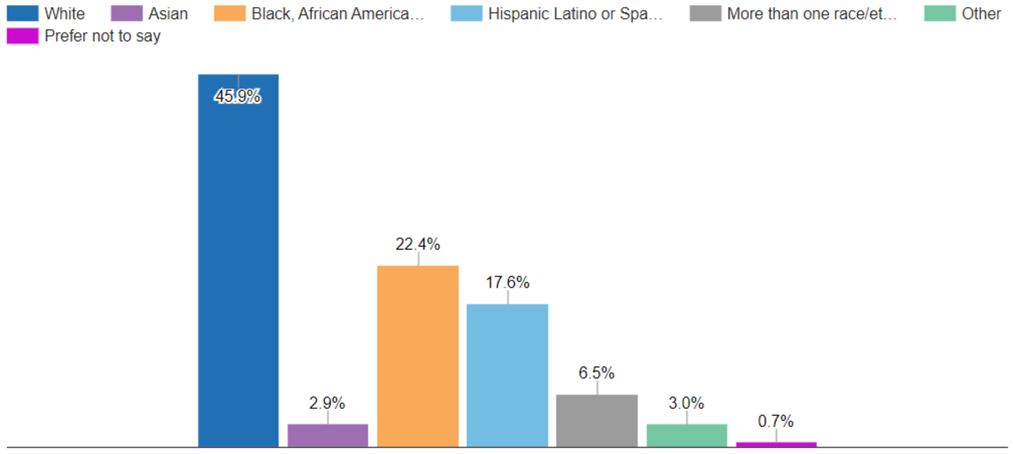
Selected Data Snapshots

(Updated 10/21/19)

Gender Identity



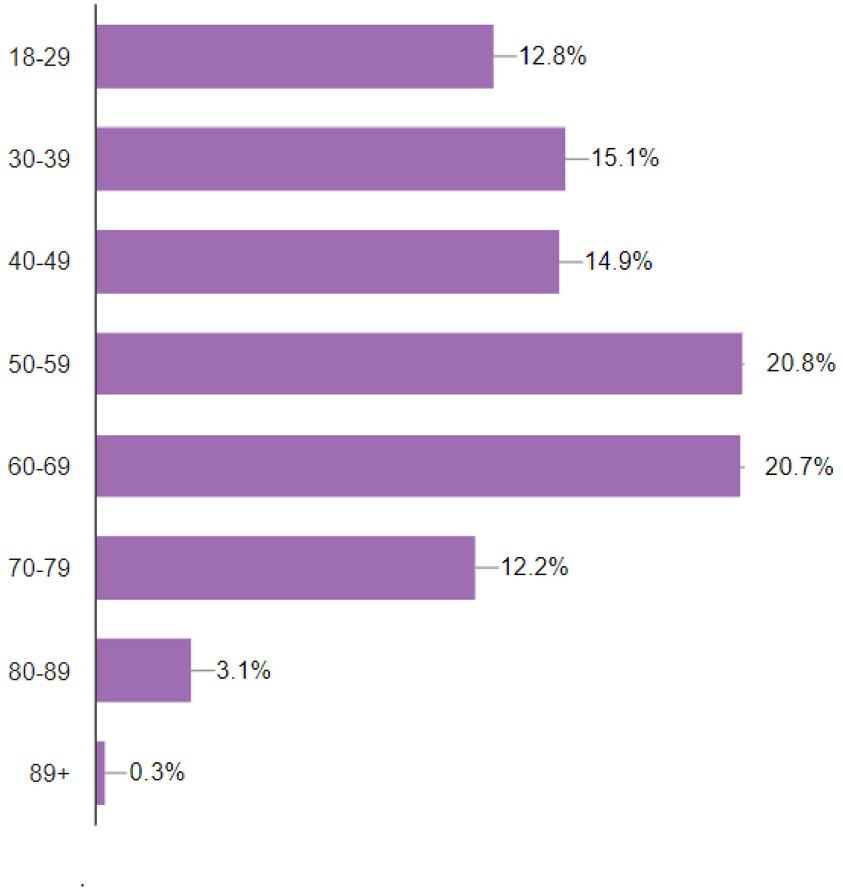
Race & Ethnicity



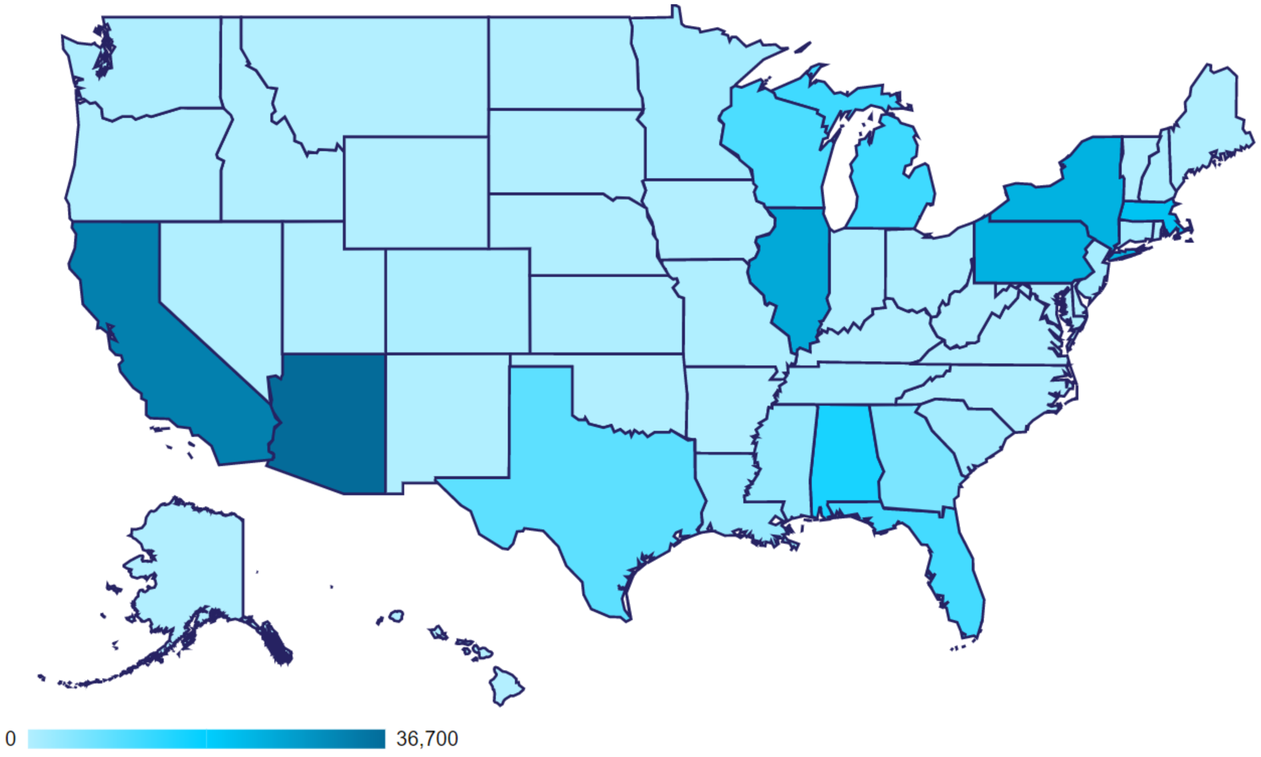
Selected Data Snapshots

(Updated 1/12/20)

Age



Geography



All 50 states
Bilingual enrollment
Interactive mobile exhibits

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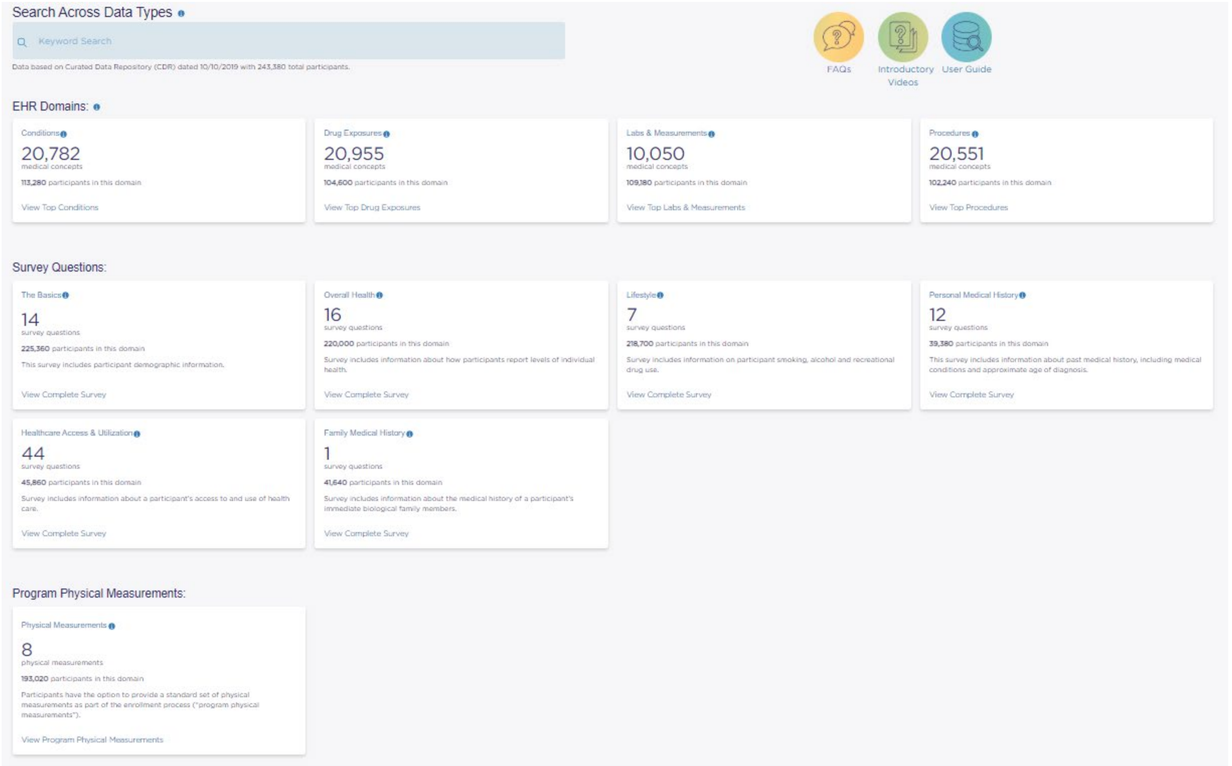
All of Us Data Browser

- Interactive tool launched in beta on May 6, 2019
  - Provides summary statistics from the program's growing database
  - Open to everyone – no login!
  - Allows participants to understand the makeup of the cohort
  - Allows researchers to understand the characteristics of our participant population, explore the data types available, plan research questions



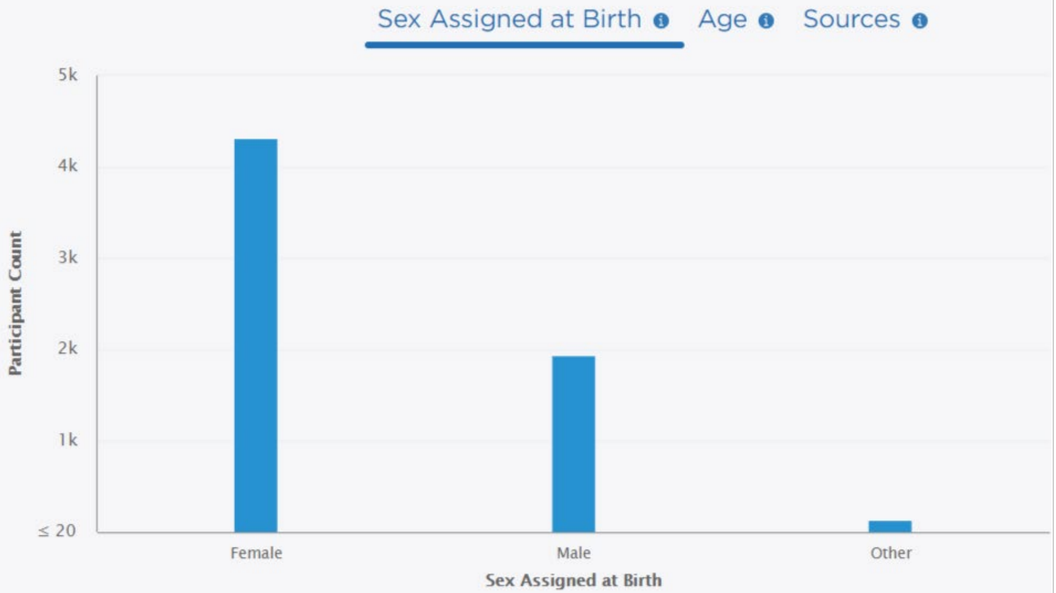
- Visit: **DataBrowser.ResearchAllofUs.org**

A Quick Look at the Data Browser

Explore data breakdowns by sex assigned at birth & age.

Drug Exposures	Participants of 33,440	% of 33,440	Vocabulary Code
1. Acetaminophen 325 MG / Hydrocodone Bitartrate 5 MG Oral Tablet	6,320	18.9%	RxNorm 857002

Also Known As APAP 325 MG / hydrocodone bitartrate 5 MG Oral Tablet



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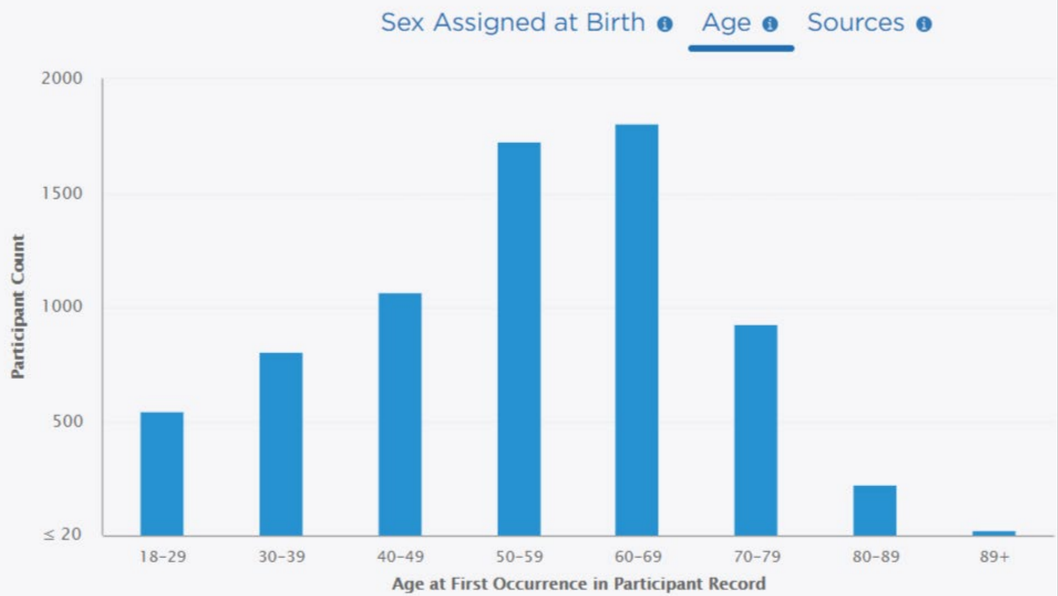

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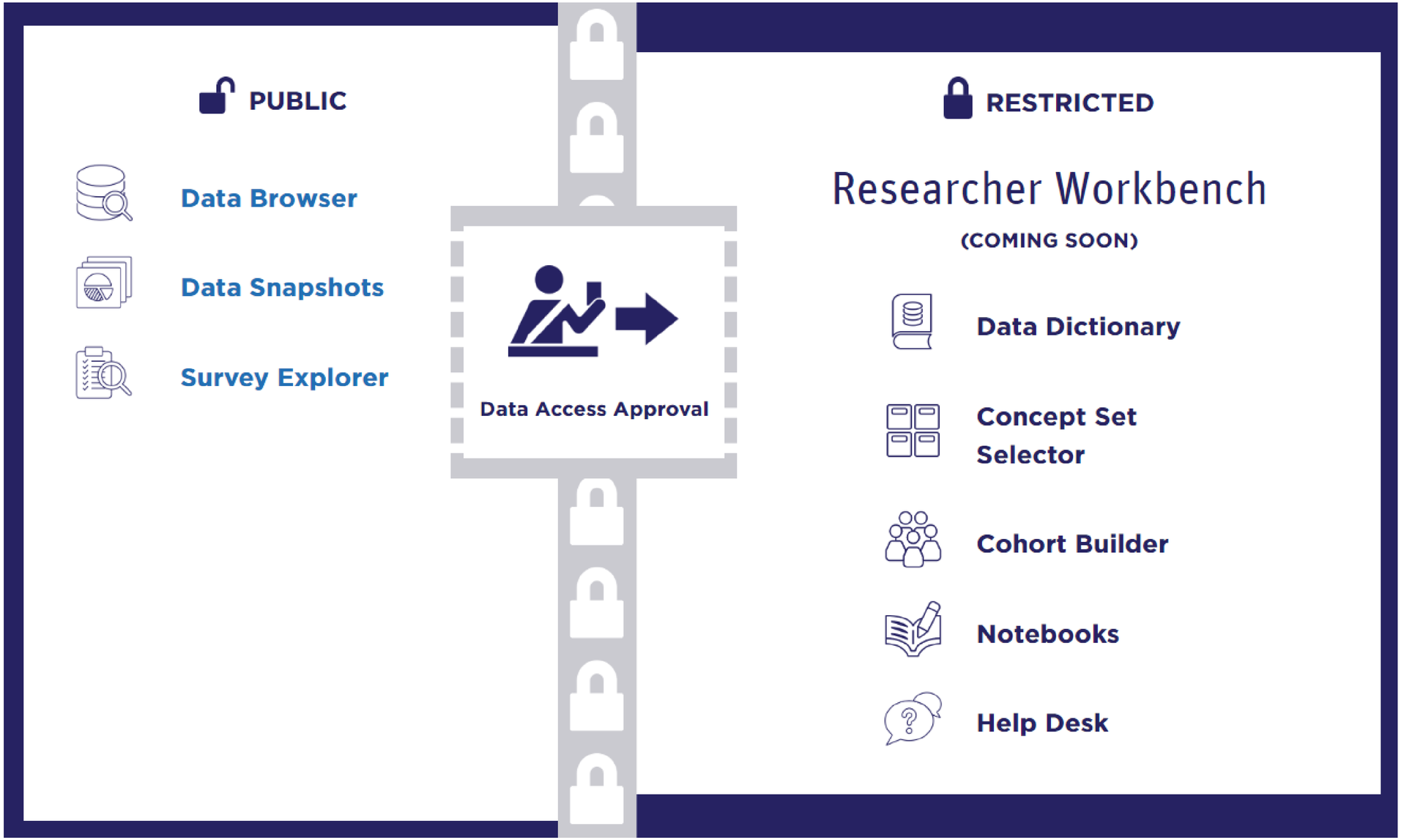
Coming Soon to the Research Hub: The Researcher Workbench



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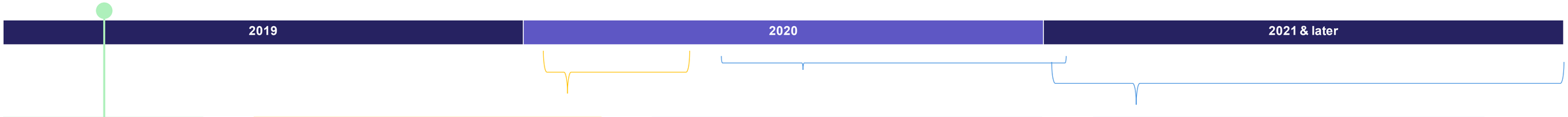
Data Release Timeline



Data Browser Launch
May 6, 2019

Launch of an interactive tool available to the public that provides summary statistics from the program's growing database.

Researcher Workbench Beta Launch
2020

Release of the first version of the *All of Us* dataset and the first set of researcher tools. The dataset will include:

- Survey data
- Measurement data
- Electronic health record (EHR) data

Additional Data Types
Late 2020

Expand the *All of Us* dataset with additional survey, measurement, and EHR data.

Add additional data types over the course of the year, including:

- Wearables data (such as Fitbit)
- Linkage to one external data type, such as the National Death Index

Additional Data Types and Tools
2021 & beyond

Expect to enroll 1M participants within 5-6 years of launch.

Continue to expand the *All of Us* dataset with new data releases, including genomics data, new surveys, assay data, and potentially linkages to external data sources, etc.

Release new versions of Researcher Workbench with more tools.

**All of Us* is targeting a bold timeline. Projected dates are subject to change and dependent on security and usability testing.

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What is the Potential for Participants?

- An opportunity to help **fight disease** and improve the health of future generations.
- A chance to **learn about your own health**, including personalized risk factors or exposures.
- The ability and choice to **access your own data**, including increasingly rich health records.
- An opportunity to **ensure that your community is included** in the studies that lead to new understanding and new treatments.
- A chance to **learn about additional research opportunities** that may interest you.
- The choice to **meet others like you**, perhaps even joining some of them to propose & do research.

All of Us RESEARCH PROGRAM

This is a long-term relationship: the value to participants and researchers will grow over time.

What is the Potential for Researchers?

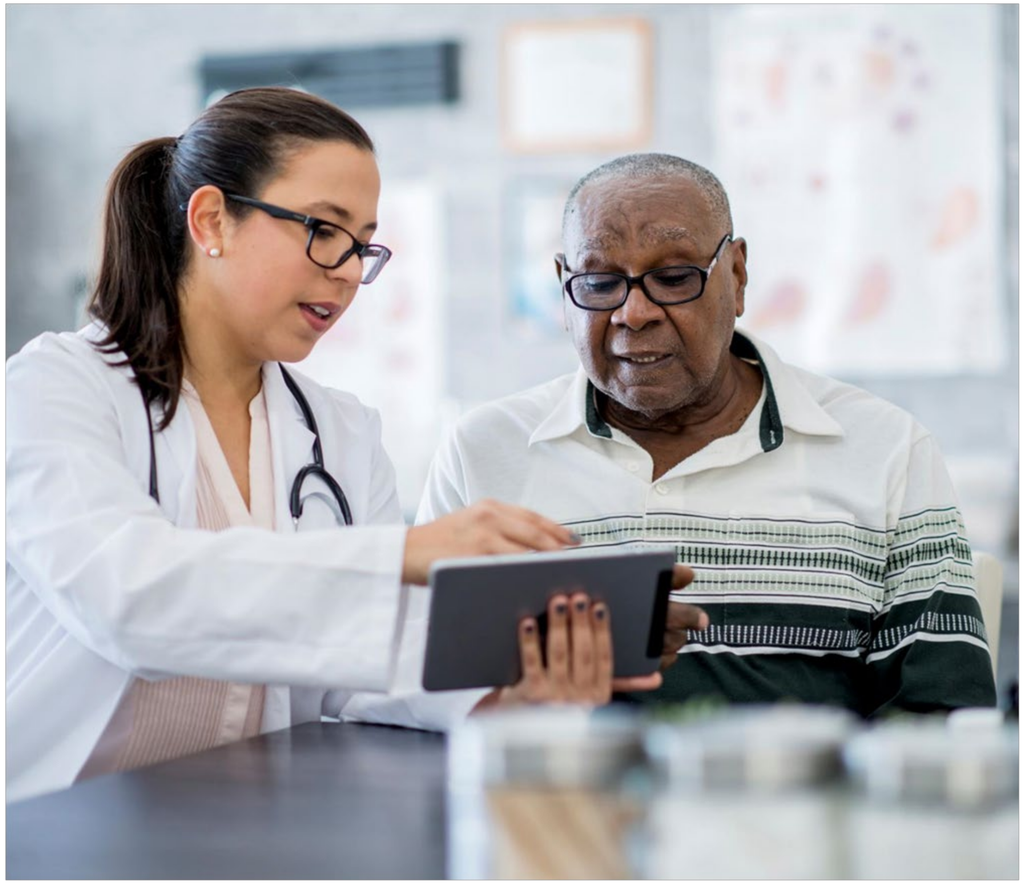
- The opportunity to **save time and resources** and **accelerate research breakthroughs** by leveraging:
  - A **rich resource of data**, including biospecimens and electronic health records.
  - A **longitudinal dataset** that will follow participants as they move, age, develop relationships, get sick, and try treatments.
  - A **diverse cohort of participants**, including people both healthy and sick, from all walks of life and all parts of the country.
  - Both raw data and data that is already **cleaned and curated**.
  - **Robust computing and analytic tools** to support complex data analyses in a **secure data environment**.
  - A group of **engaged participants** who may be eager to participate in ancillary studies.
- The ability to easily **share workspaces and analyses** with research partners and reviewers.
- The chance to learn from the program's pilots and experiments and **leverage innovations** for other studies and cohorts.

All of Us RESEARCH PROGRAM

This is a long-term relationship: the value to participants and researchers will grow over time.

What is the Potential for Providers?

- Over time, **increased scientific evidence and improved guidelines** to enable precision medicine opportunities for more people and conditions:
  - Better understanding of the **impact of environment and lifestyle factors** on health.
  - Increased knowledge of differences in risk factors and response to treatments among **diverse populations**.
  - More information on the development of conditions that will allow for **earlier detection**.
  - Deeper understanding of different conditions that may allow for **better stratification**.
- Innovations that may make it easier to **share electronic health records** with other providers and patients.
- New knowledge to help address **health disparities**, increase **patient engagement**, and understand the usefulness of **consumer health devices and apps**.



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Limitations

- Not nationally representative
- Data will be continuing to expand in depth and breadth as the program grows
- Not all participants will have all data types available

Conclusions

- Assembling the most diverse large-scale cohort of its kind with plans for genomic data and comprehensive clinical information
- Successfully engaging participants as partners
- New data types continuing to be rolled out
- Ancillary studies of specific populations or disease states possible
- Will facilitate research across multiple disease states and could serve as controls for disease-specific studies that lack healthy controls

It takes *All of Us*….

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For more information…

ResearchAllofUs.org
(includes the Data Browser)
JoinAllofUs.org

@AllofUsResearch
#JoinAllofUs

AllofUs.nih.gov

Questions?