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

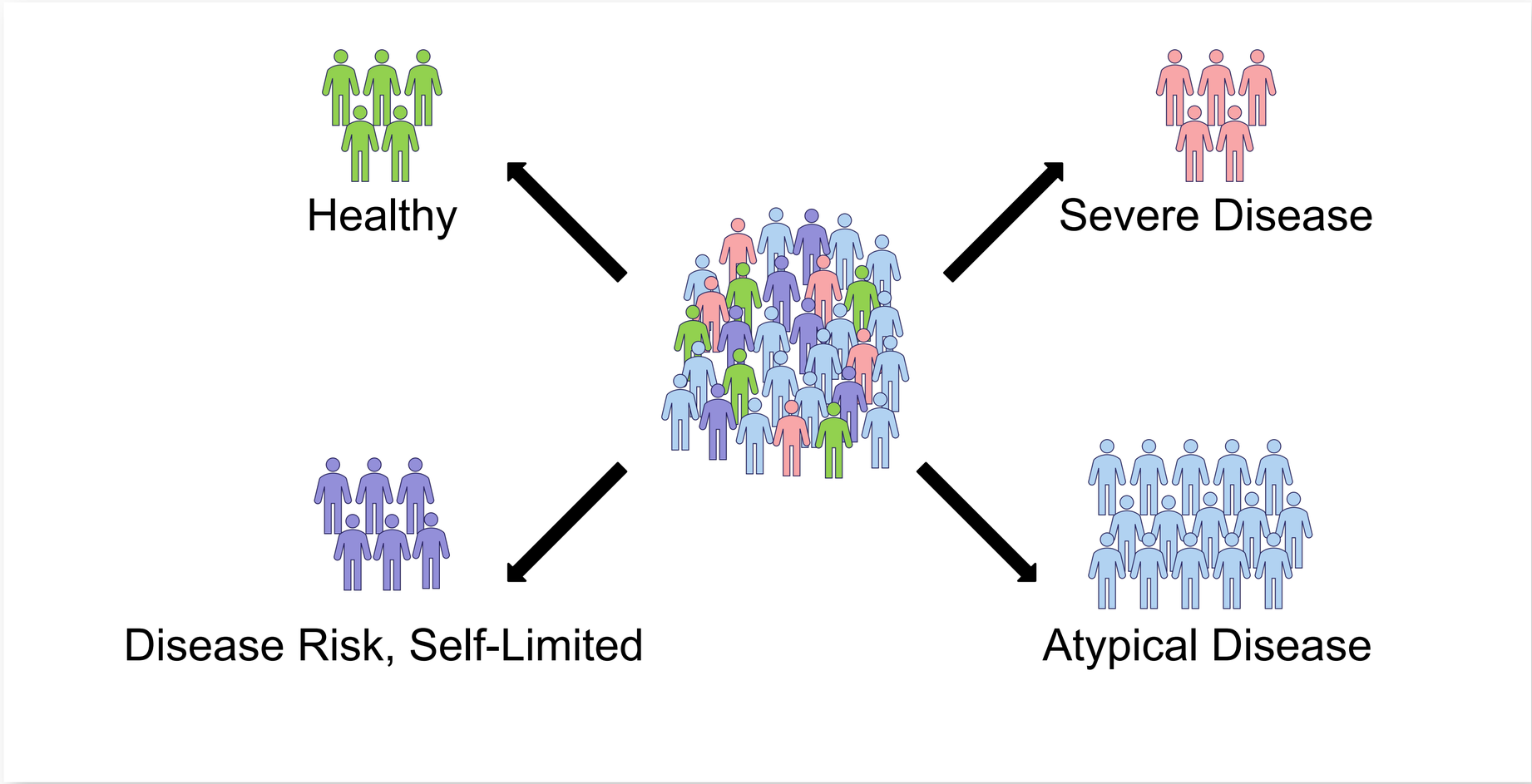
September 30, 2021

Josh Denny, MD, MS
Chief Executive Officer
All of Us Research Program

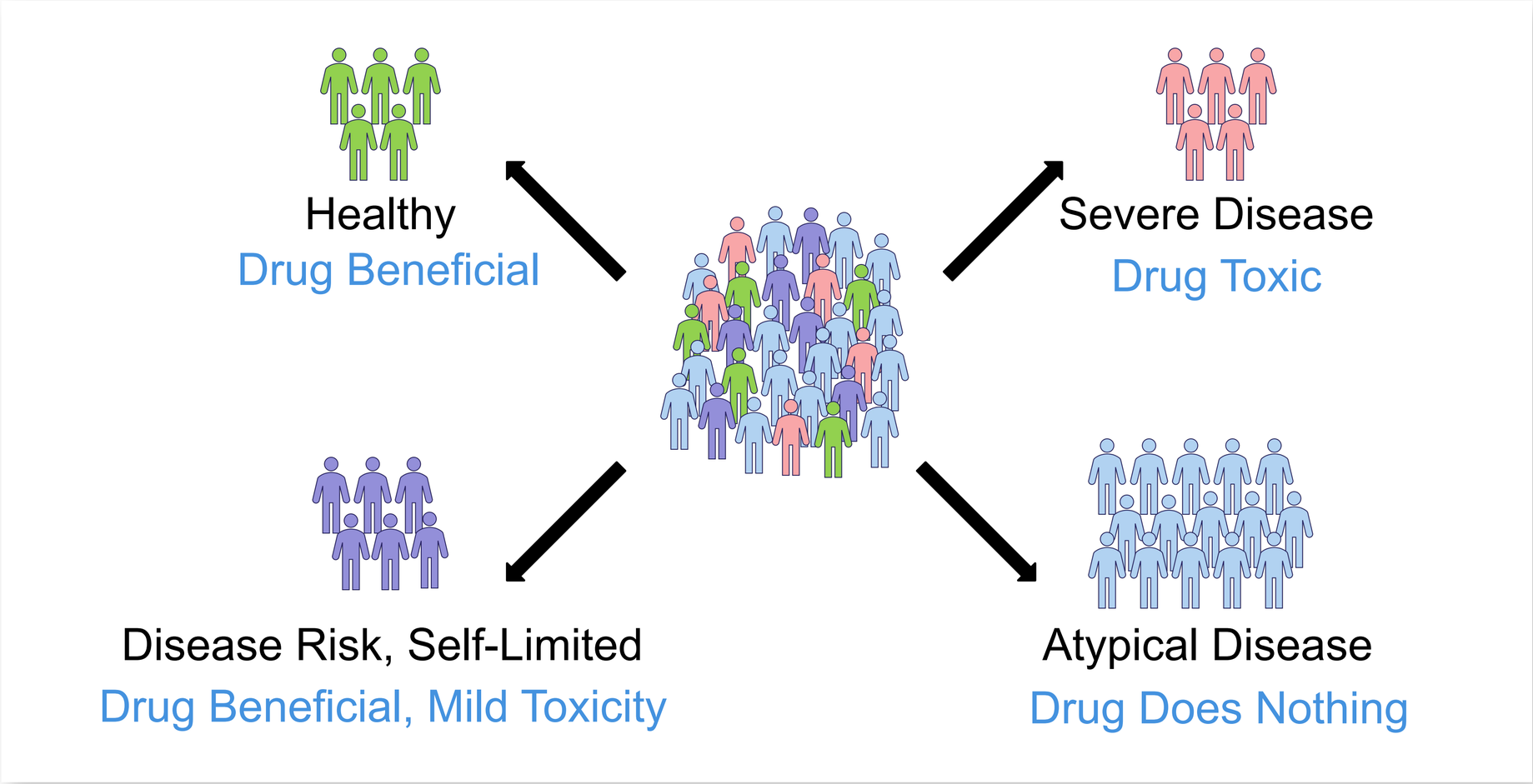
@AllofUsCEO

National Institutes of Health

People Have Different Disease Risks

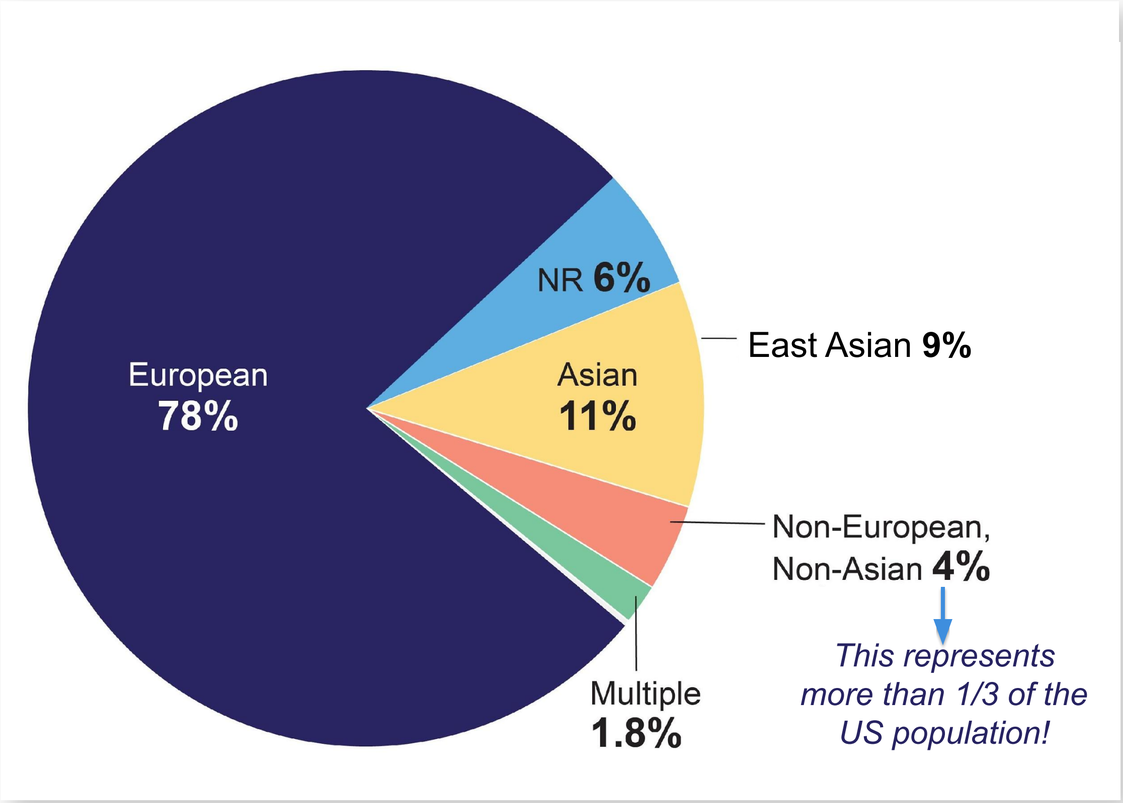


People Have Different Disease Risks and Variable Drug Responses

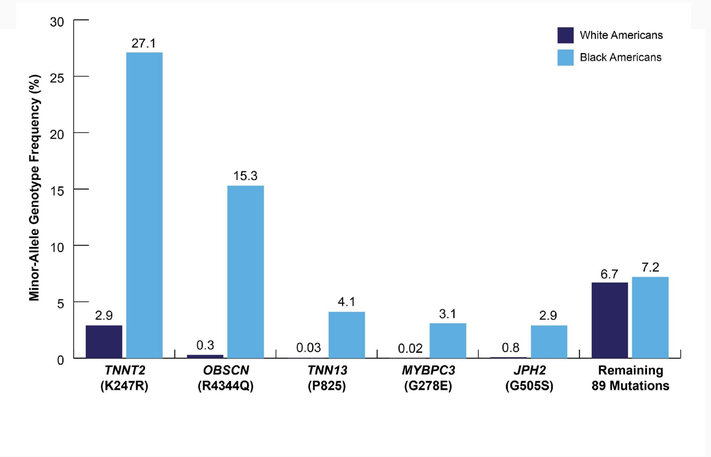


There is a Lack of Diversity in Genomic Studies

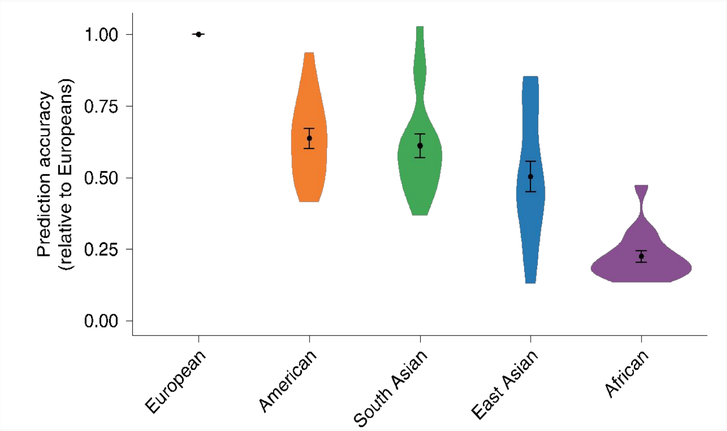
There is a lack of diversity in genome-wide association studies.



This affects interpretation of genetic variants...



... polygenic risk scores for diseases

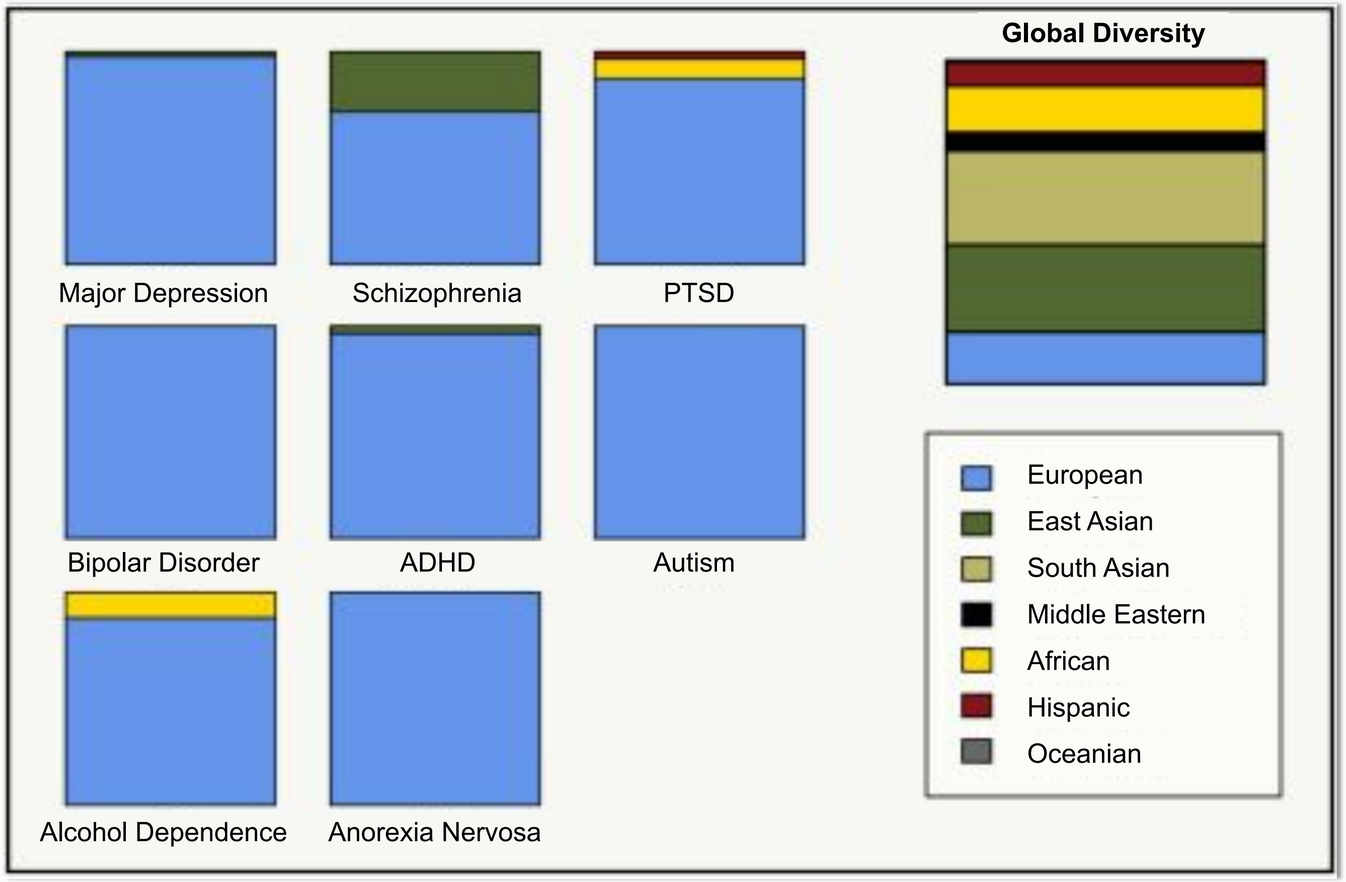


… and many other impacts

Morales *et al.*, *Genome Biol*, 2018; Martin et al., *Nat Genetics,* 2019; Manrai et al., *NEJM,* 2016

There is a Lack of Diversity in *Psychiatric* Genomic Studies also

Diversity in GWAS of Psychiatric Disorders Compared to Global Diversity



Peterson, *et al.*, *Cell*, 2019

This lack of diversity in psychiatric genomic studies results in a poor understanding of disease mechanisms and effective treatment options for all populations.

All of Us Research Program Mission

Nurture relationships

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

Our mission

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

Deliver one of the largest, richest biomedical dataset

that is secure and easy to access

Catalyze a robust ecosystem

of researchers and funders hungry to use and support it

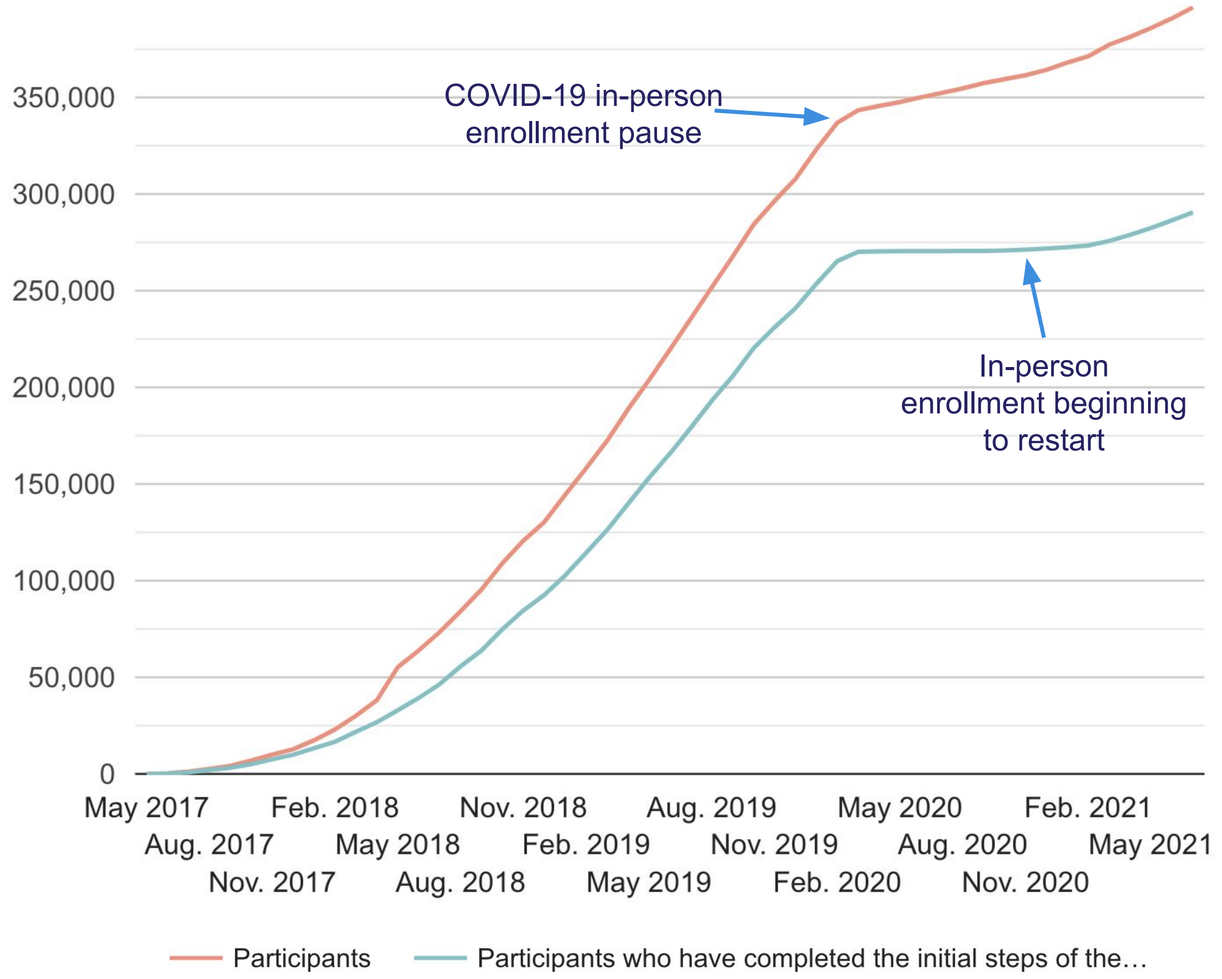
Status of the *All of Us* Research Program (as of September 21, 2021)

411,000+
Participants

253,000+
Electronic Health Records

297,000+
Participants who have completed initial steps of the program

313,000+
Biosamples



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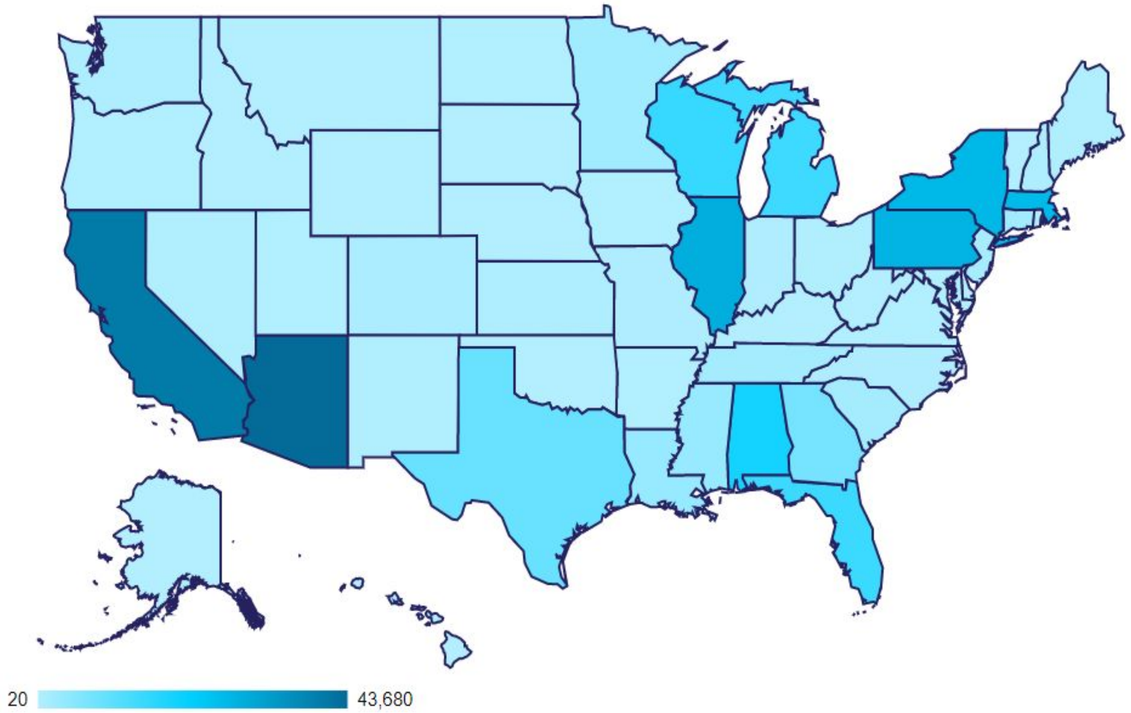
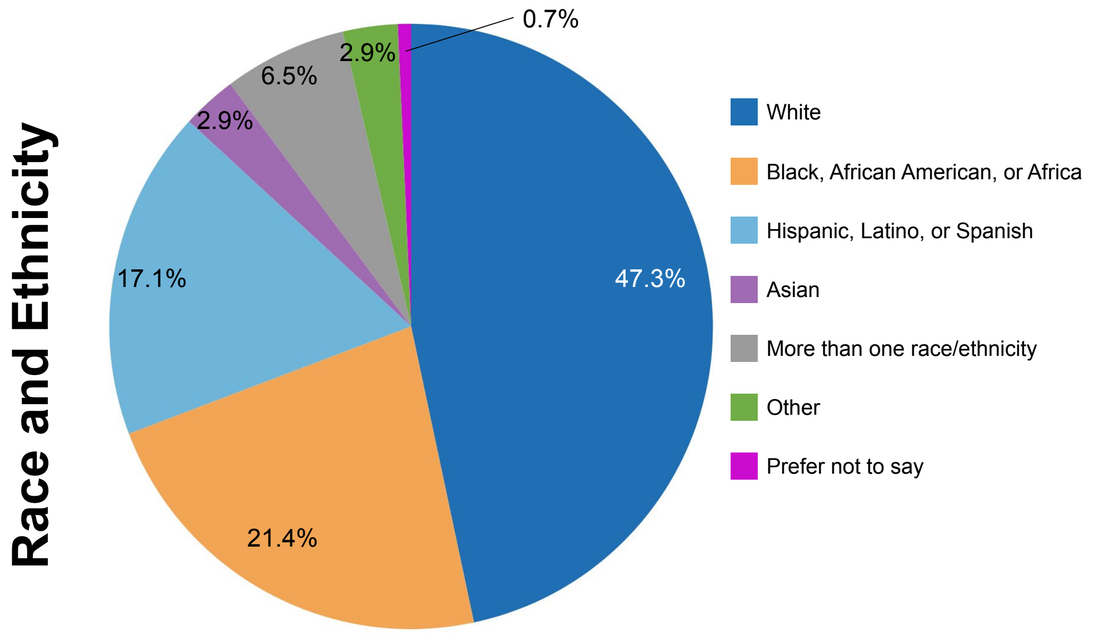
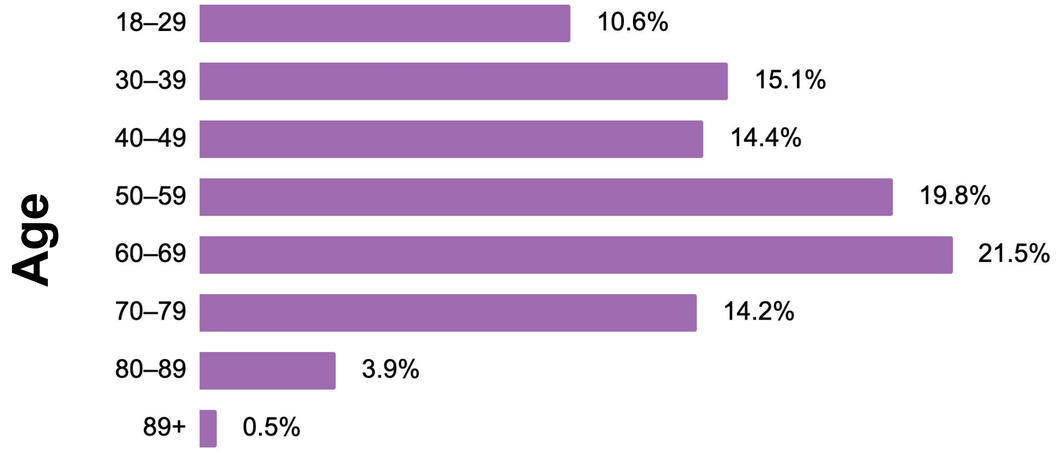


Over 80% of *All of Us* participants are underrepresented in biomedical research





researchallofus.org

Data Collected from *All of Us* Participants

- Consent and Electronic Health Records
- Participant Surveys
- Physical Measurements
- Biosamples
- Mobile/Wearable Tech

Data Collected from *All of Us* Participants: Surveys

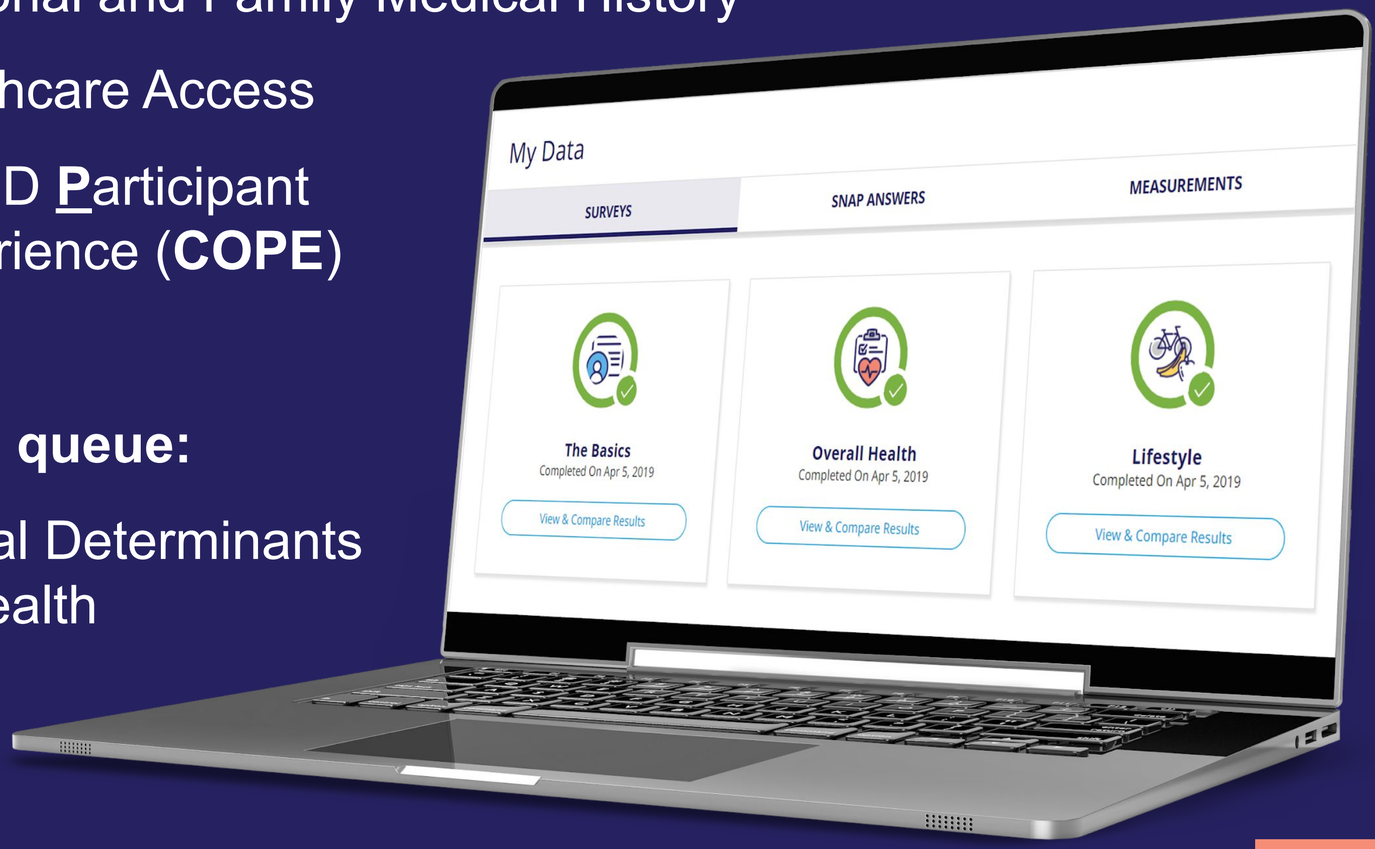
- Consent and Electronic Health Records
- **Participant Surveys**
- Physical Measurements
- Biosamples
- Mobile/Wearable Tech

Current surveys focused on:

- Demographics and Lifestyle
- Personal and Family Medical History
- Healthcare Access
- **CO**VID **P**articipant **E**xperience (**COPE**)

Next in queue:

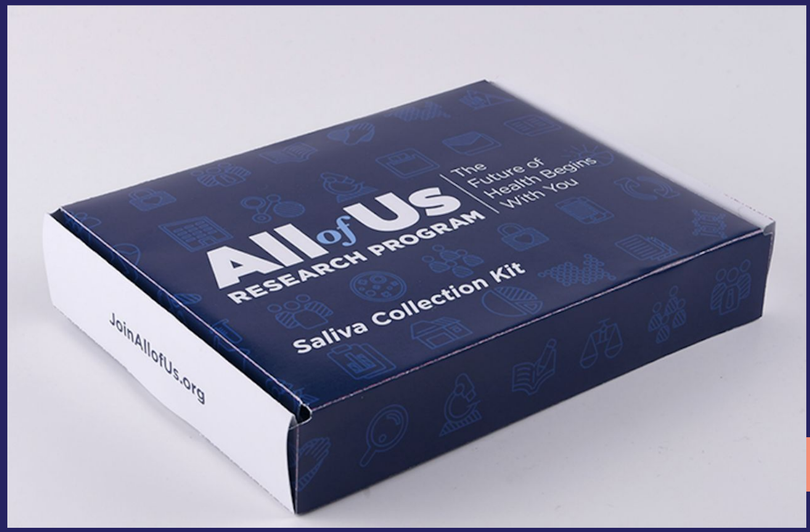
- Social Determinants of Health



Data Collected from *All of Us* Participants: Biosamples

- Consent and Electronic Health Records
- Participant Surveys
- Physical Measurements
- **Biosamples**
- Mobile/Wearable Tech

- Blood
  - DNA
  - RNA
  - cfDNA
  - Serum
  - Plasma
- Saliva kits (if not blood)
- Urine



Returning Value to *All of Us* Participants

Returning Value for Participants: Genetic Information

Non-Health Genetic Traits

Traits

Genetic Ancestry

Currently Returning to Participants

>56,000 participants viewed traits/ancestry results

Health-Related Genetic Traits

Hereditary Disease Risk (ACMG59)

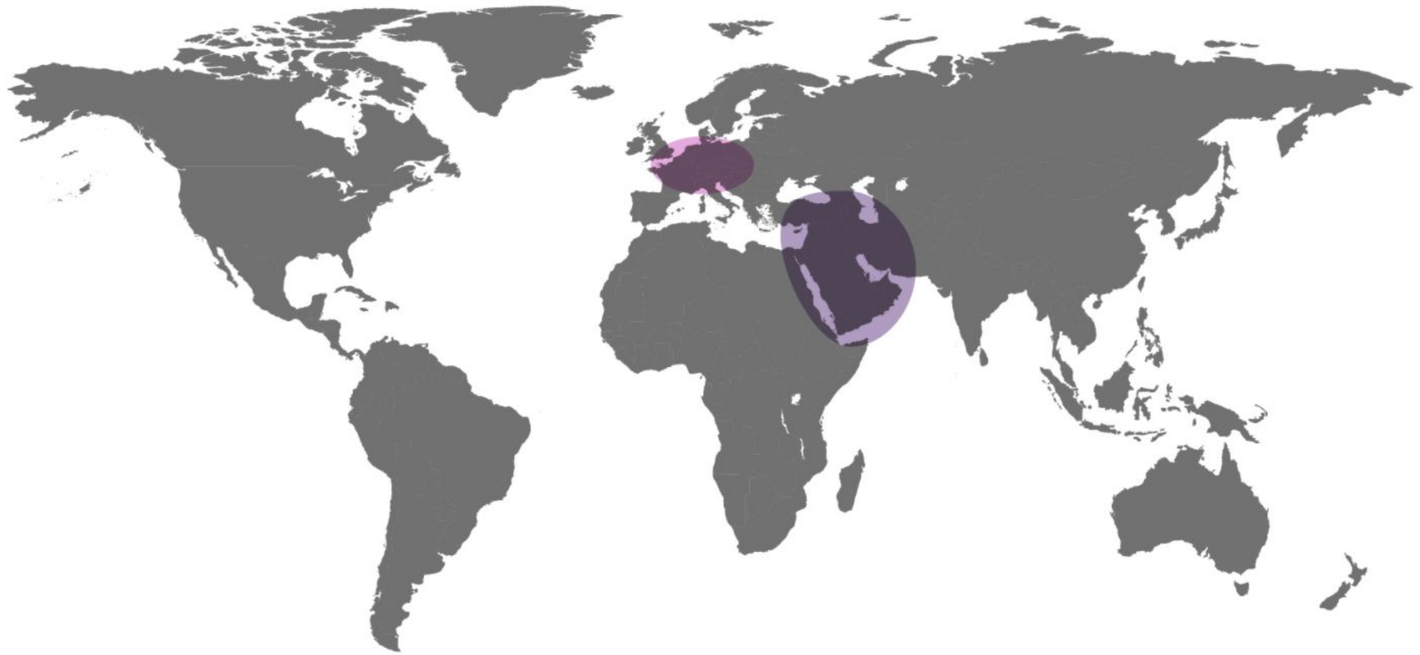
Medicine and Your Health (Pharmacogenomics)

Launching in 2022

Genetic Ancestry Results

The Middle East and North Africa	50%
The Middle East Such as the Arabian Peninsula and Egypt	**50%**

Europe	50%
All tested populations	



The Middle East and North Africa

This genetic ancestry group represents people from these areas:

- The Middle East
- North Africa
- Western Asia
- The Caucasus

Connections near and far

People with recent ancestors from Asia, Europe, and sub-Saharan Africa may have patterns of DNA from this genetic ancestry group. This is likely because of significant trade and migration through the region that continues to this day. The Silk Road and Incense Route connected the Middle East and North Africa to Europe and Asia. Trans-Saharan trade routes connected North Africa to sub-Saharan Africa.

Non-Health Trait Results

Ancestry

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

Traits

Bitter taste perception
Learn what your genes can tell you about your ability to taste bitter things.

Cilantro preference
Smell and taste work together to influence your cilantro preference.

Earwax type
Flaky or sticky? Earwax type is encoded in your genes.

Lactose intolerance
Your genes code for lactase, which helps you digest milk.

Cilantro preference

Some people like the taste of cilantro and others think it tastes like soap.

What we looked at and why

We looked at a place in your DNA that influences if you have a slightly higher chance of liking or disliking cilantro.[1] The percent of people across the world who dislike cilantro ranges from 3-21%.[2]

- **People who have slightly higher chances of liking cilantro** may find it fragrant and citrusy.
- **People who have slightly higher chances of disliking cilantro** may find it soapy or moldy.

This place in your DNA only predicts a small amount of your chances of liking or disliking cilantro. Environmental and other genetic factors also play a role.

DNA Marker*	Gene	Your result*
rs72921001	*Near OR6A2*	C A

* Each of your parents provides you with a nucleotide at this position, but we don't know which parent gave you which nucleotide.

Scientific details

OR6A2 makes a sensor in the nose that helps us perceive smells. Changes near *OR6A2* may impact whether you find cilantro fragrant and citrusy, or soapy or moldy.[1]

Health-Related Genetic Trait Return of Results: Medicine and Your DNA

All of Us RESEARCH PROGRAM

JANE DOE
DOB: May 25, 1977
ID: 123456

Specimen: Blood
Barcode: 223 234234 2343
Collected: September 15, 2018
Report date: October 2, 2018

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. Some genes help break down medicines and clear them from your body. Some genes even change medicines into a form that makes them work properly.

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.

IMPORTANT!

- **If your doctor has prescribed medicine for you, keep taking it.** It can be dangerous to stop taking a medicine, or to change the dose or timing of it, without first asking your doctor.

Genetic information is really just one piece of the puzzle.

In the DNA and medicine section of your results, you'll see a list of medicines that may be impacted by your genetics. Changes in some genes influence how certain medications work in the body.

A lot of other things may affect how someone's body reacts to a medicine. These include other medicines you may be taking, your health history, and your lifestyle.

Health-Related Genetic Trait Return of Results: Medicine and Your DNA

Your Results:

Gene
CYP2C19

The *CYP2C19* gene is a "metabolizer" gene. These genes play a role in how quickly or slowly medicines are used, or metabolized, by the body.

Version
*2/*2

What it means
Poor metabolizer

A poor or likely poor metabolizer gene may cause the body to process medicines at a much slower rate than normal. If so, some medicines may **stay in the body for a longer amount of time than expected.** This could increase the risk of side effects from these medicines.

Gene
DPYD

The *DPYD* gene is a "metabolizer" gene. These genes play a role in how quickly or slowly medicines are used, or metabolized, by the body.

Version
*1/*1

What it means
Normal metabolizer

A **normal metabolizer** gene may cause the body to process medicines at an average rate. If so, some medicines may **stay in the body for the usual amount of time.** The medicines work the way we expect them to.

Gene
SLCO1B1

The *SLCO1B1* gene helps move some medicines out of the body when they are done working. People with changes in this gene may have a harder time removing these medicines from their body. This means those medicines may build up in the body and cause muscle pain.

Version
*1/*5

What it means
Decreased function

A **"decreased function"** version of this gene may act at a rate that is much slower than average. This means certain medicines may **increase a person's risk of developing muscle pain.**

Genetics and medicine
DNA and medicine

These medicines MAY BE impacted by your genetics.

In some cases, pharmacogenetic information may help doctors and pharmacists choose medicines and doses.

This table points out some medicines that may be affected by your genetic results.

If you are taking one of these medicines, talk with your doctor or pharmacist about whether ordering a clinical pharmacogenetic test is right for you.

Gene: *SLCO1B1*	1 Medicine
• simvastatin (Zocor®)	

Gene: *CYP2C19*	10 Medicines
• amitriptyline (Elavil®)	
• clobazam (Onfi®)	
• clomipramine (Anafranil®)	
• clopidogrel (Plavix®)	
• doxepin (Sinequan®)	
• escitalopram (Lexapro®)	
• imipramine (Tofranil®)	
• sertraline (Zoloft®)	
• trimipramine (Surmontil®)	
• voriconazole (Vfend®)	

Just because a medicine is listed here doesn't mean that you should or should not be taking it. Some people with these genetic results still process these medications normally.

Returning Value to *All of Us* Researchers

Researcher Data Access

Raw Data Repository

Data Curation

Data
Harmonization
Privacy
Methodology
QA/CC

Individual Biospecimen and Participant Data
(Available in the future)

Controlled Tier
(Available in the future)
No obvious PII. Genomics, Clinical Narrative data, Data Linkages, Other Data Types

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

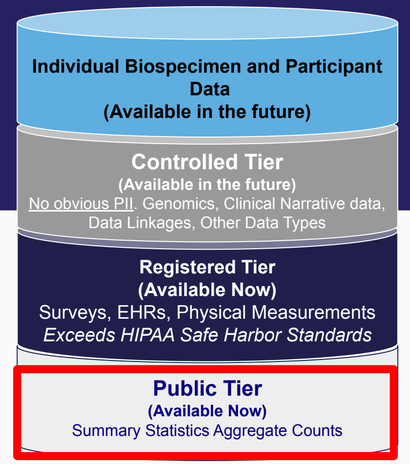
Public Tier
(Available Now)
Summary Statistics Aggregate Counts

(future) → **Future ancillary studies**
Could recontact participants, use biospecimens, issue new surveys or DHT, enroll in clinical trials

(Winter 21/22) / **(now)** → **Researcher Workbench**
ResearchAllofUs.org/Apply/

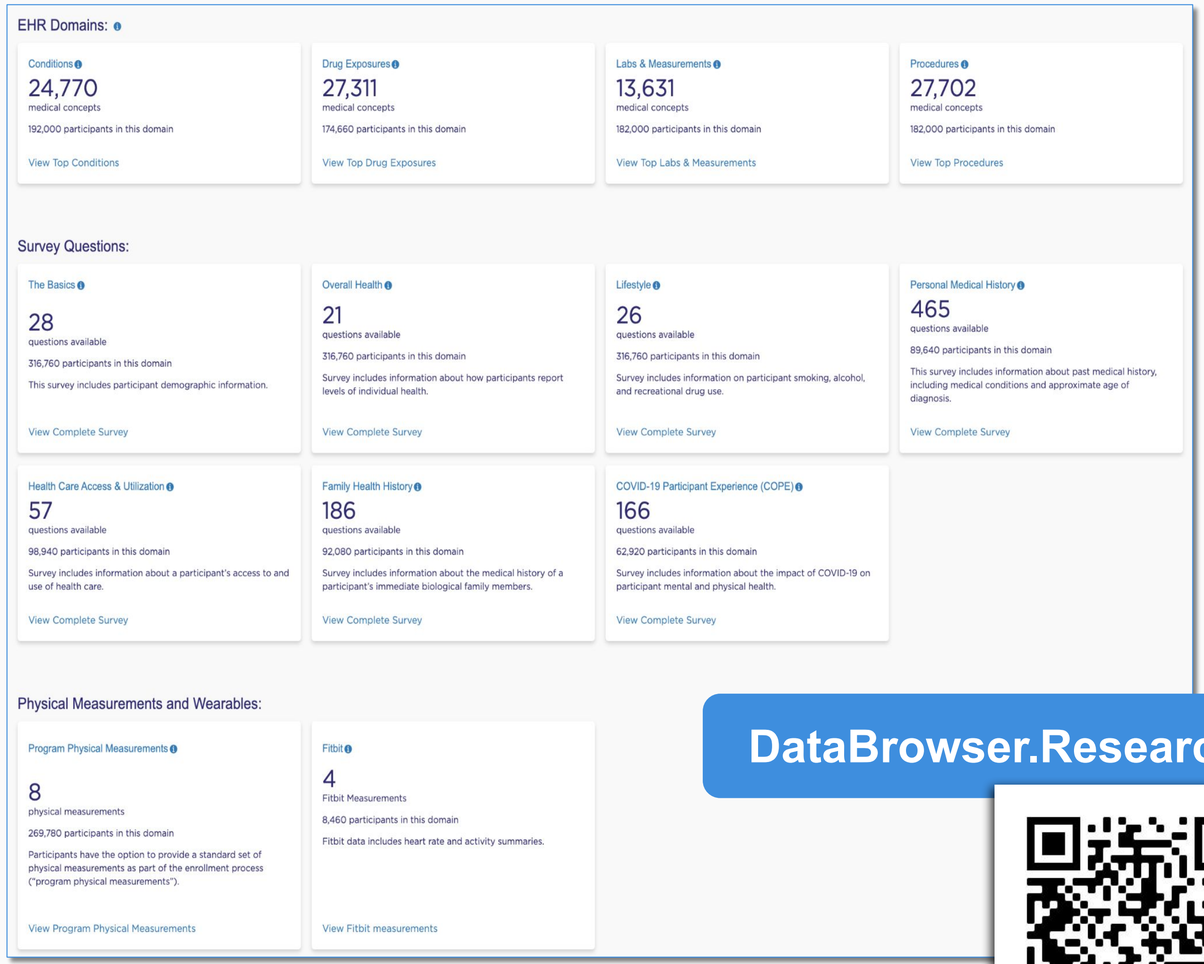
(now) → **Data Browser**
databrowser.researchallofus.org
(public, no login required)

All of Us Research Hub: Public Data Browser



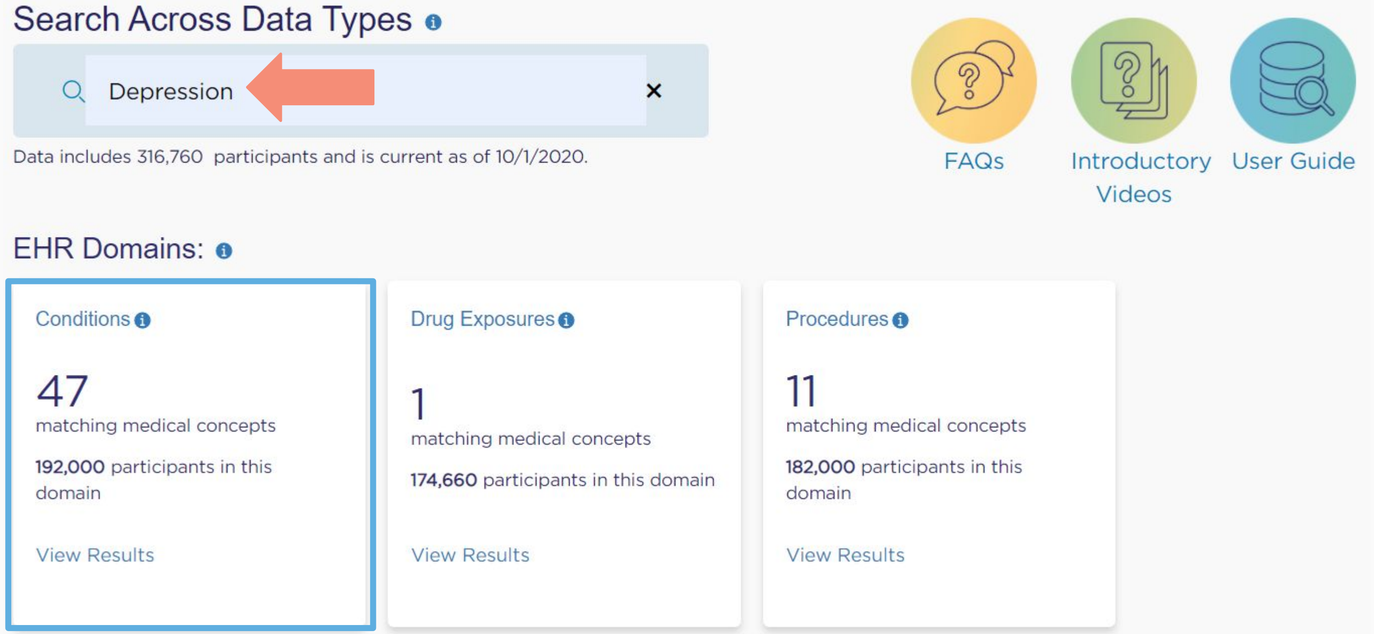
Summary statistics of participant data

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



DataBrowser.ResearchAllofUs.org

All of Us Research Hub: Data Browser – EHR Conditions



All of Us Research Hub: Data Browser – EHR Conditions

Search Across Data Types

Depression

Data includes 316,760 participants and is current as of 10/1/2020.

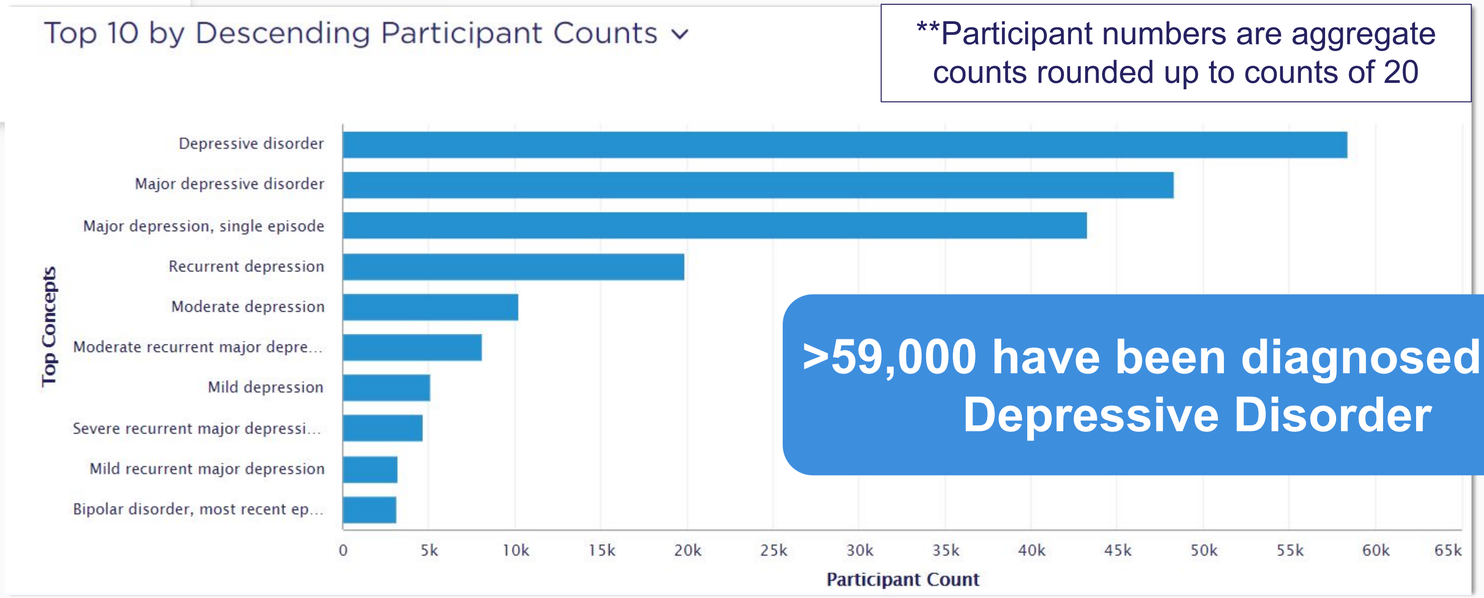
FAQs | Introductory Videos | User Guide

EHR Domains:

Conditions
47
matching medical concepts
192,000 participants in this domain
View Results

Drug Exposures
1
matching medical concepts
174,660 participants in this domain
View Results

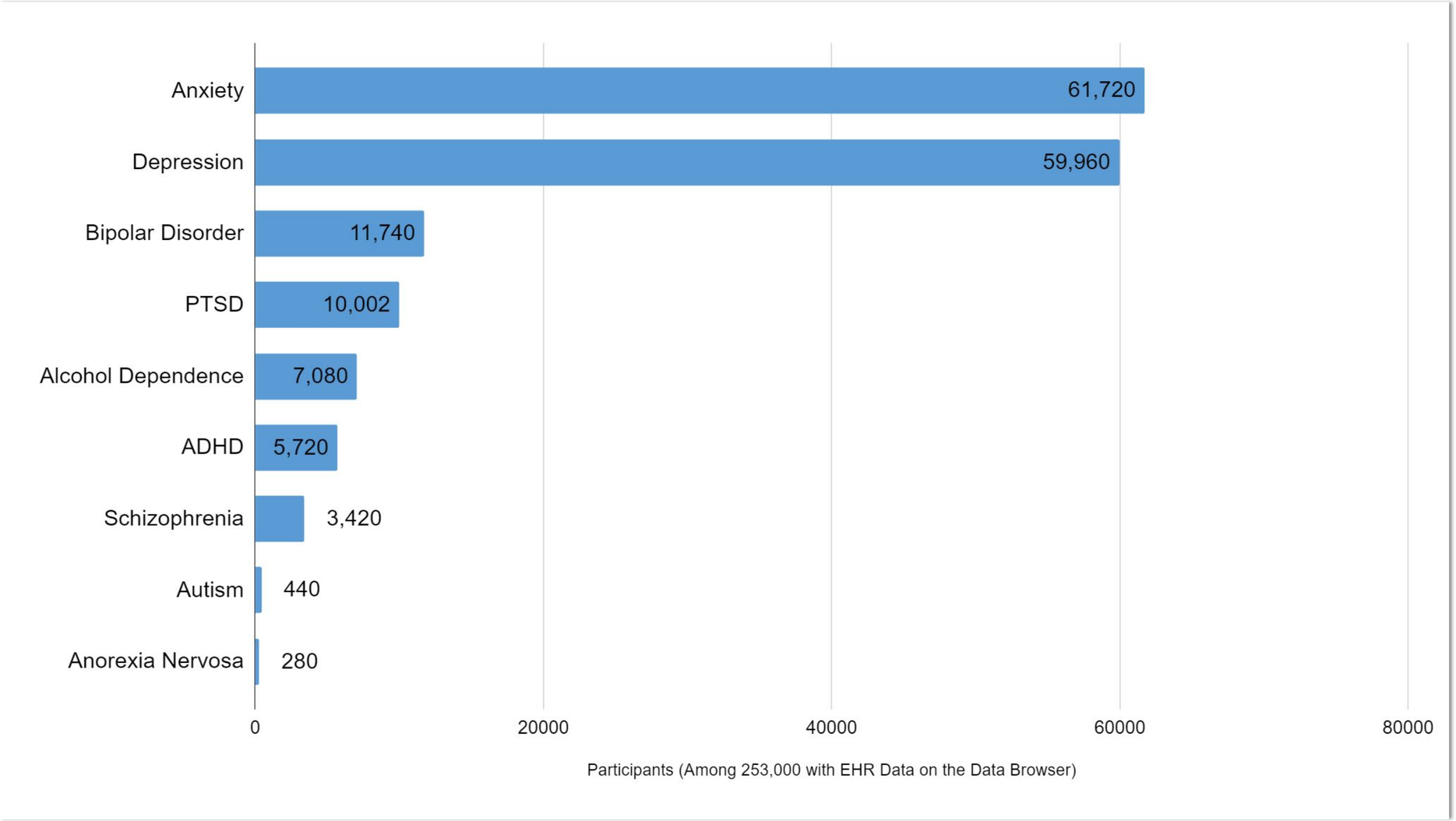
Procedures
11
matching medical concepts
182,000 participants in this domain
View Results



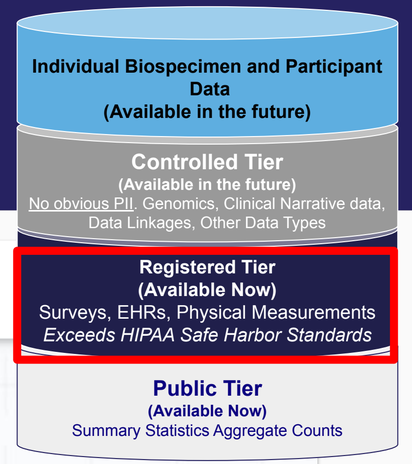
**Participant numbers are aggregate counts rounded up to counts of 20

>59,000 have been diagnosed with Depressive Disorder

All of Us Research Hub: Data Browser – EHR Conditions

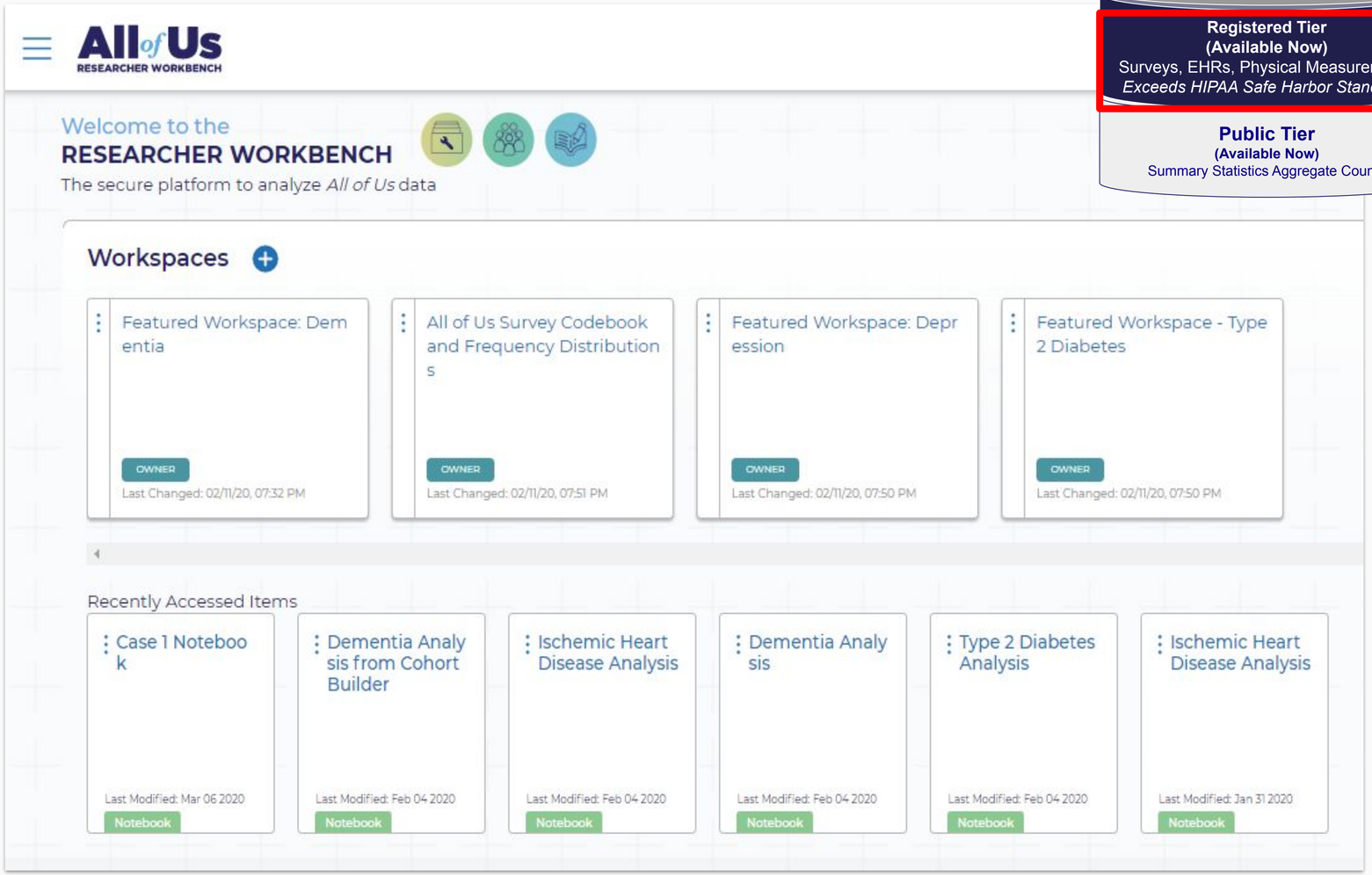


All of Us Researcher Workbench: Access to Row-Level Data for Analysis



Researcher Workbench Beta
Launched on May 27, 2020

- Cloud based central resource
- Personally-identified information is removed
- **Passport access model** - just create, describe your workspace, and get to work! No separate IRB approval needed.
- During beta phase, access limited to US nonprofits



ResearchAllofUs.org

Researcher Application Process During the *Beta* Launch

Visit ResearchAllofUs.org/Apply

STEP 1

CHECK FOR YOUR INSTITUTION'S AGREEMENT

Check that your institution has signed the Data Use and Registration Agreement. If you do not see your institution listed, please fill out the form to initiate the process.

STEP 2

REGISTER AS A RESEARCHER

Complete your researcher profile, sign Terms of Services, and agree to the the Privacy Policy. Please note, a Data Use and Registration Agreement must be in place, and you must have an eRA Commons account.

STEP 3

CONNECT eRA COMMONS

Connect your eRA Commons account upon applying to the Researcher Workbench.

STEP 4

COMPLETE *All of Us* RESPONSIBLE CONDUCT OF RESEARCH TRAINING

Understand more about our privacy safeguards and the ethics surrounding the use of participant data.

STEP 5

SIGN AUTHORIZED USER CODE OF CONDUCT

Each user must agree and sign an Authorized User Code of Conduct

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This process takes about ~2 hours of a researcher's time – then you're on!

Researcher Workbench: By the Numbers *(Since Launch in May 2020)*

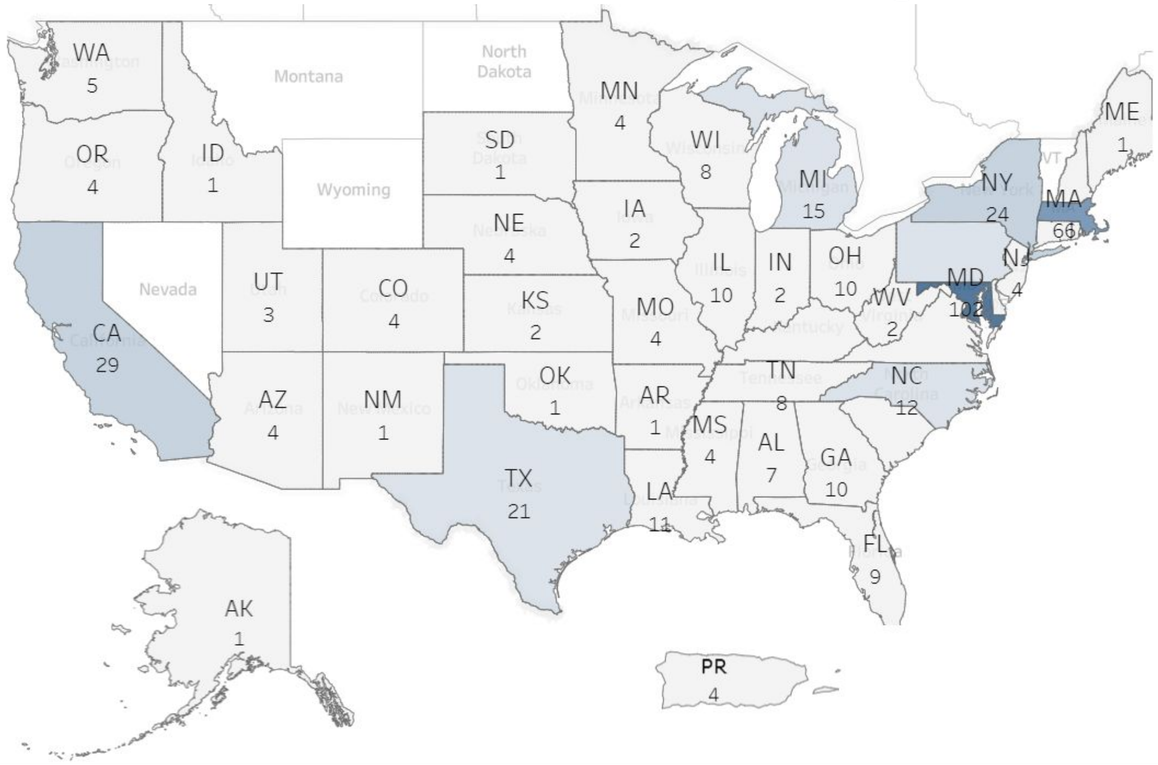
Research on the Researcher Workbench

1100+
Registered Researchers

700+
Active Projects

21+ Publications
using *All of Us* data

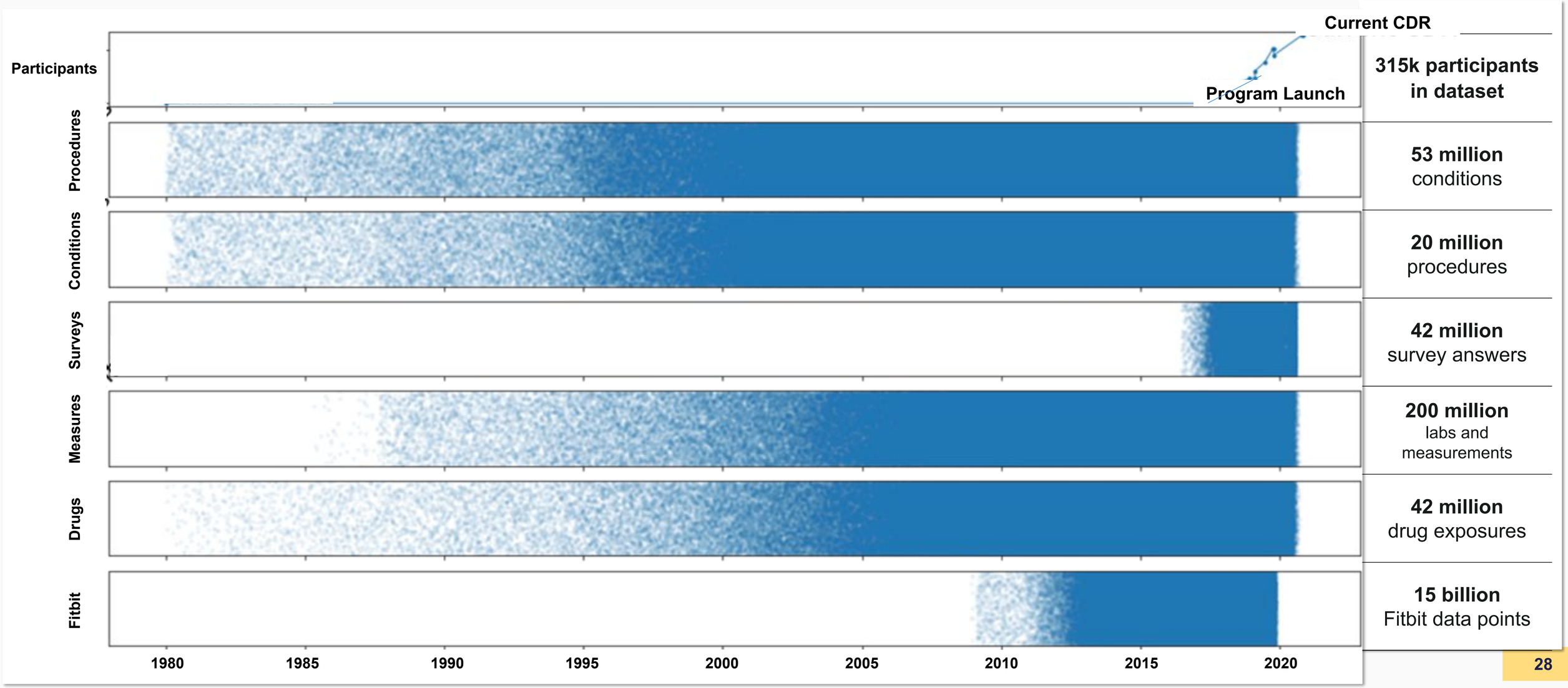
Institutional Agreements



More than 240 registered institutions

Over 24% are Historically Black Colleges and Universities, Hispanic Serving Institutions, or Non-Profits

Participant EHRs and Fitbit Provide Longitudinal Data



COVID-19 Serology Study Published in *Clinical Infectious Diseases* (June 15, 2021)

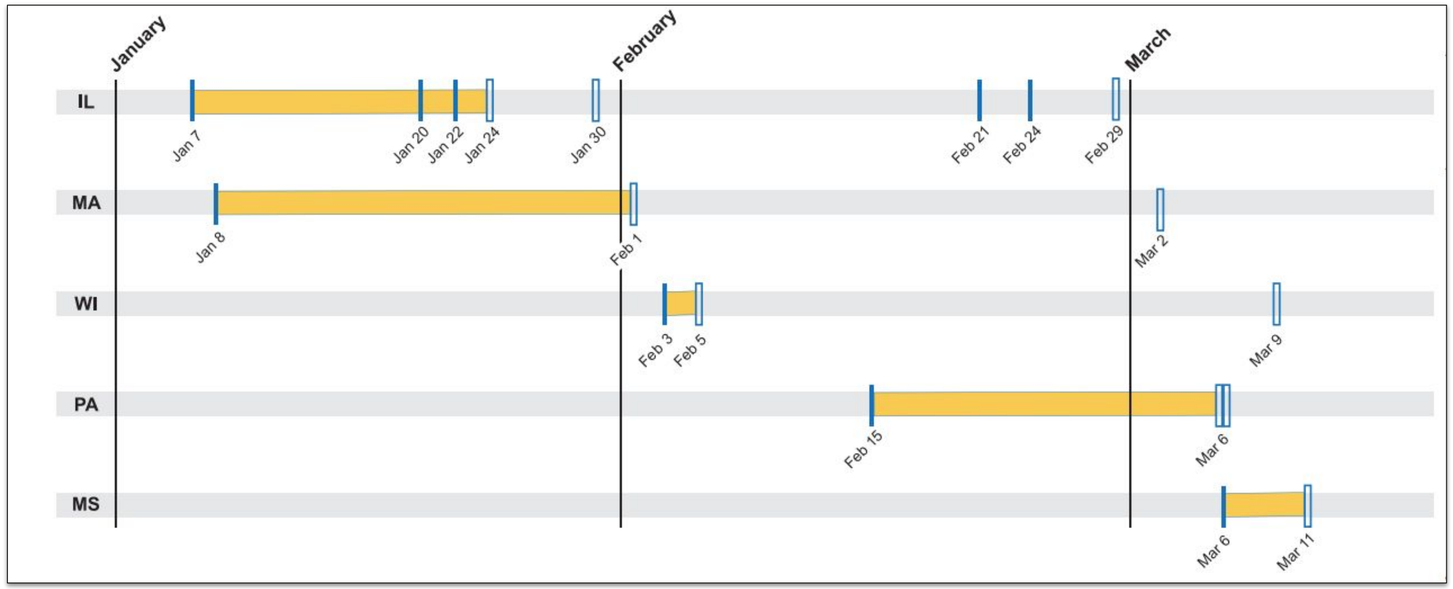
OXFORD ACADEMIC

Clinical Infectious Diseases

ACCEPTED MANUSCRIPT

Antibodies to SARS-CoV-2 in *All of Us* Research Program Participants, January 2-March 18, 2020 FREE

Keri N Althoff, PhD, MPH ✉, David J Schlueter, PhD, Hoda Anton-Culver, PhD, James Cherry, PhD, Joshua C Denny, MD, MS, Isaac Thomsen, MD, MSCI, Elizabeth W Karlson, MD, MS, Fiona P Havers, MD, MHS, Mine S Cicek, PhD, Stephen N Thibodeau, PhD ... Show more



9 cases in 5 states (IL, MA, WI, PA, MS) in 24,079 tested samples

7 earlier than known cases in those states

Earliest case January 7, 2020

Returned results to participants

***All of Us* Team member handles participant samples in the lab**

Press Coverage of the *All of Us* COVID-19 Serology Study

Sections | The Washington Post — Democracy Dies in Darkness | Carolyn Denny

Health

NIH study suggests coronavirus may have been in U.S. as early as December 2019

The Coronavirus Outbreak › | Maps and Cases | States Falling Behind Vaccine Goals | Vaccine Maps | Vaccines and Children

Scientists Report Earliest Known Coronavirus Infections in Five U.S. Sta

Blood drawn from nine people in the earliest days of the pandemic tested positive for the infection. But some experts questioned the results.

THE WALL STREET JOURNAL.

U.S.

Covid-19 Ranged From Illinois to Massachusetts Before States Reported First Cases

Blood samples show people in five U.S. states were infected early,

CNN health | LIVE TV

NIH researchers find more evidence Covid was circulating in the US in December 2019

By Maggie Fox, CNN

Updated 1:57 PM ET, Tue June 15, 2021

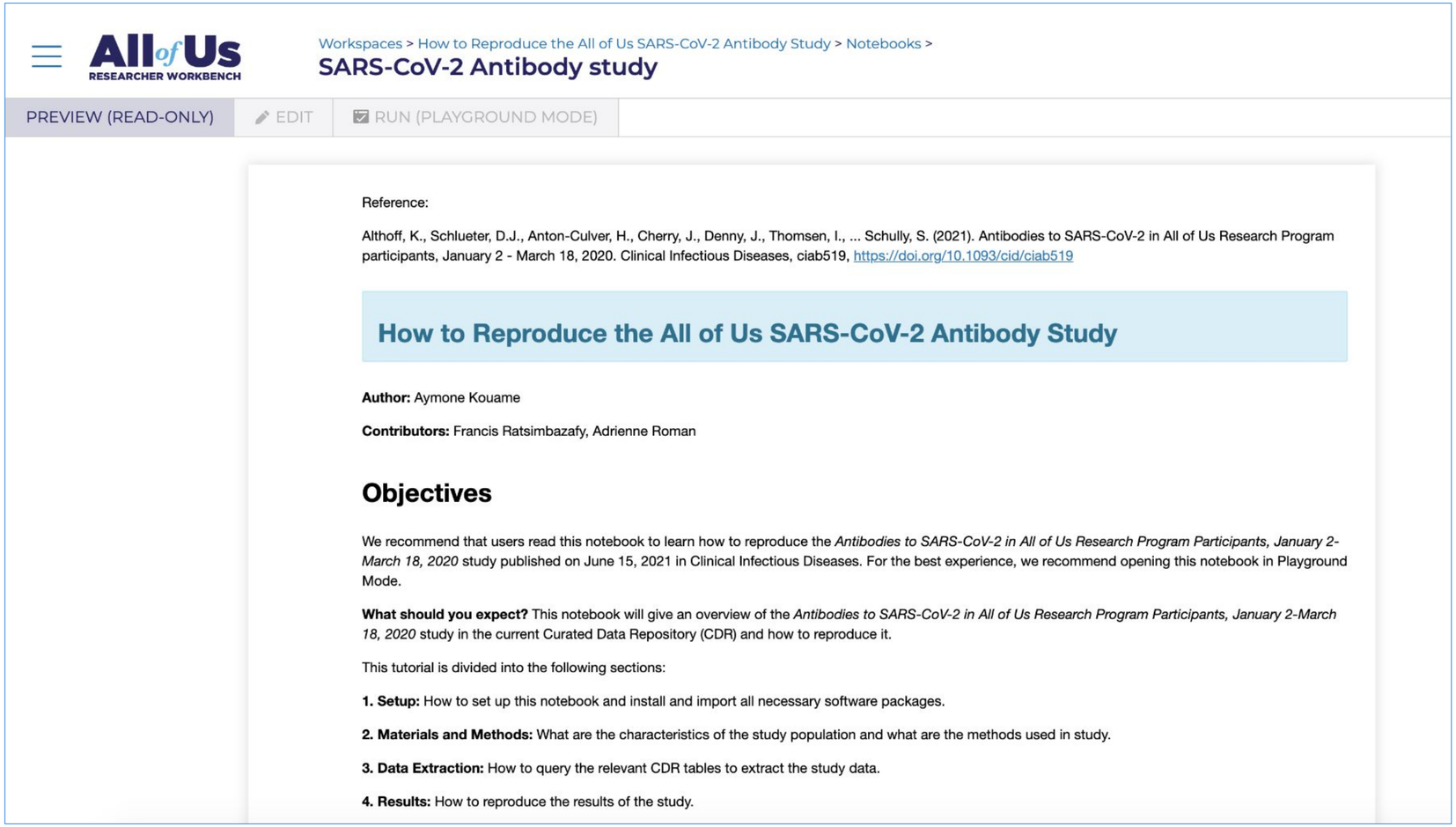
AP | More evidence suggests C... | Top Stories | Topics | Video | Listen

More evidence suggests COVID-19 was in US by Christmas 2019

By MIKE STOBBE June 15, 2021

Click to copy

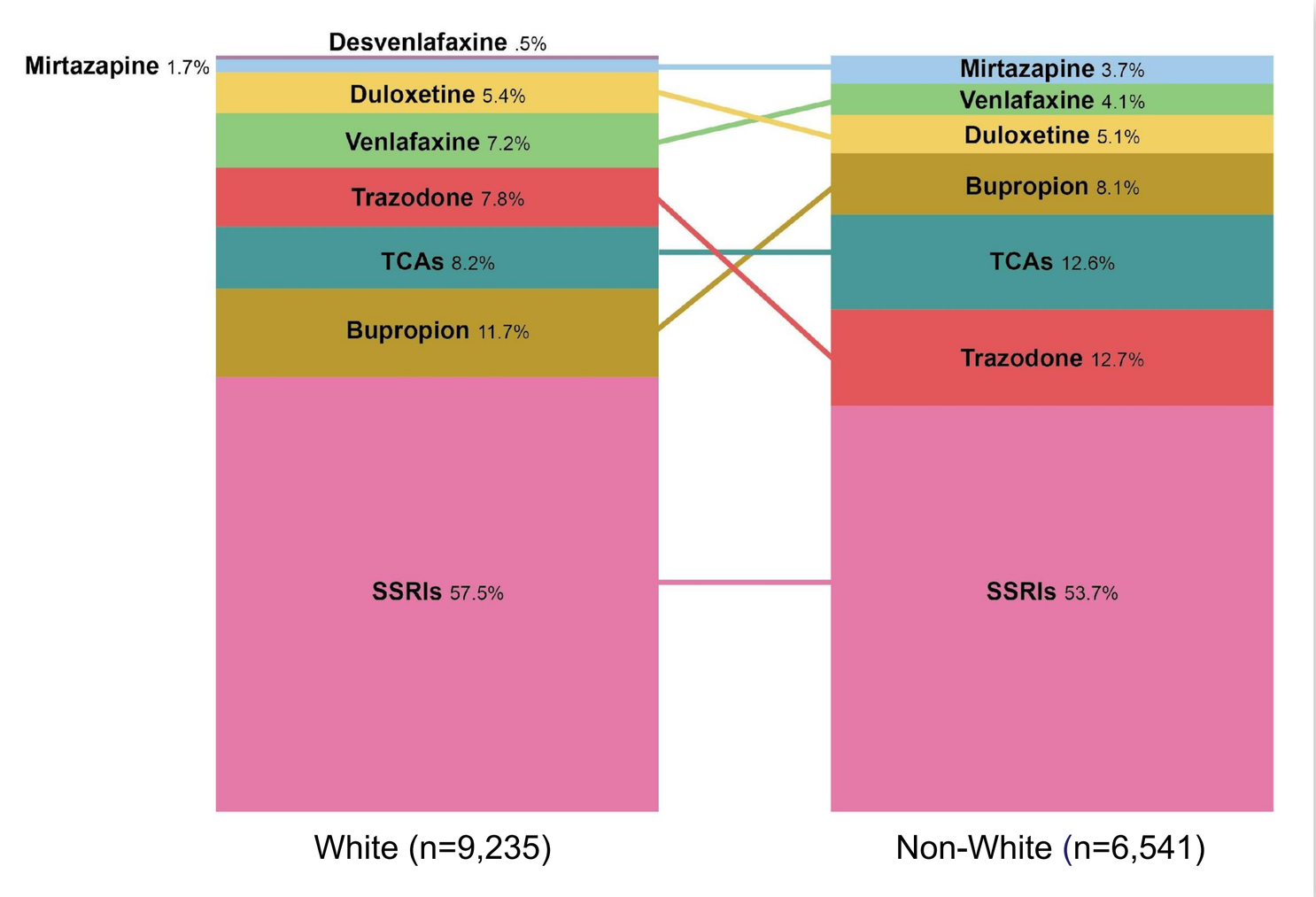
Making Research Reusable & Reproducible: *All of Us* Analysis Can Be Accessed by Any Other *All of Us* Researcher

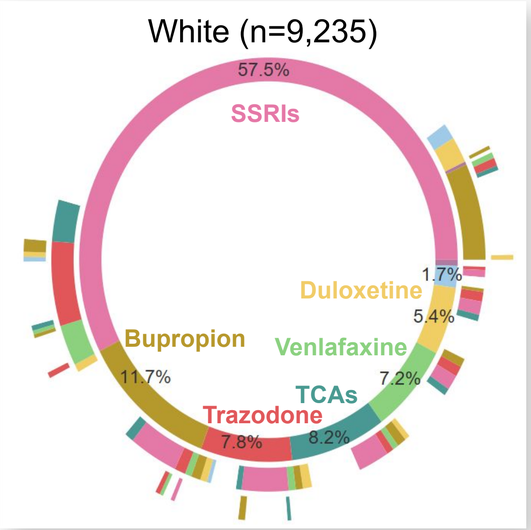


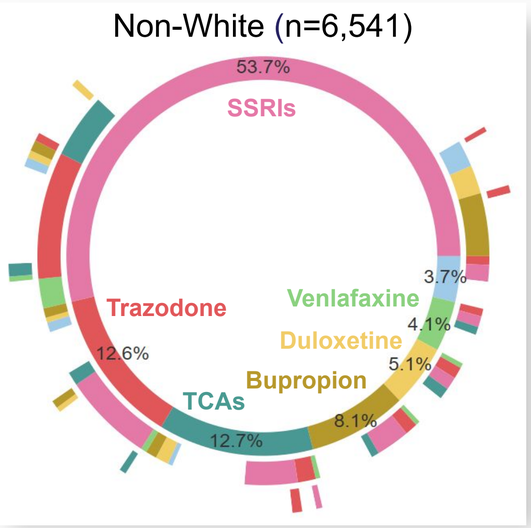
[Notebook URL: https://bit.ly/3h7GnEF](https://bit.ly/3h7GnEF)

Any *All of Us* researcher can review and reuse the exact data and analyses used in the paper

Demonstration Project: Antidepressants Taken by Participants with Depression







https://bit.ly/3zRCABL

COVID-19 Participant Experience (COPE) Survey

Self-report survey covering topics:

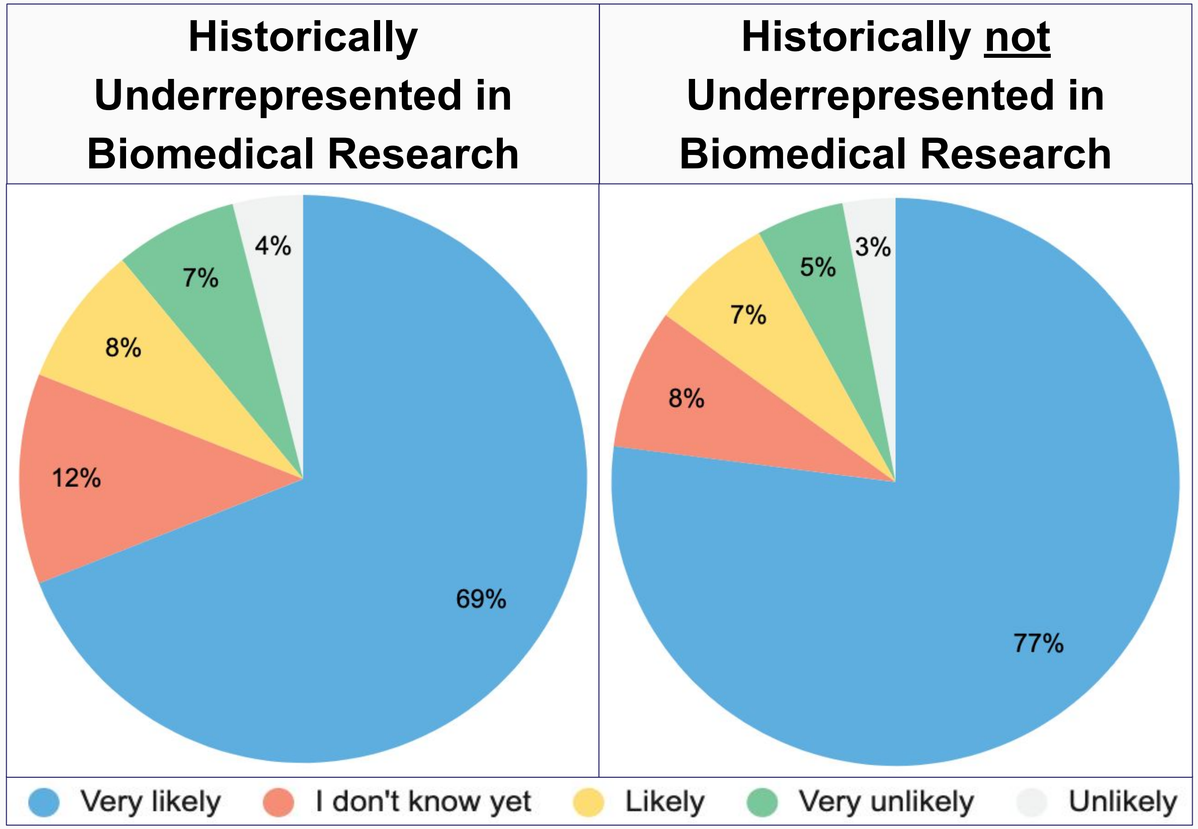
- COVID symptoms, testing, treatment
- COVID vaccine experiences
- Physical activity
- Mental health and well-being (including GAD-7, PHQ-9)
- Social support
- Substance use
- Resilience
- Discrimination

Repeated 6 times from May 2020 to February 2021

99k participants with >275k responses to the six COPE surveys (among >330k participants in CDR)

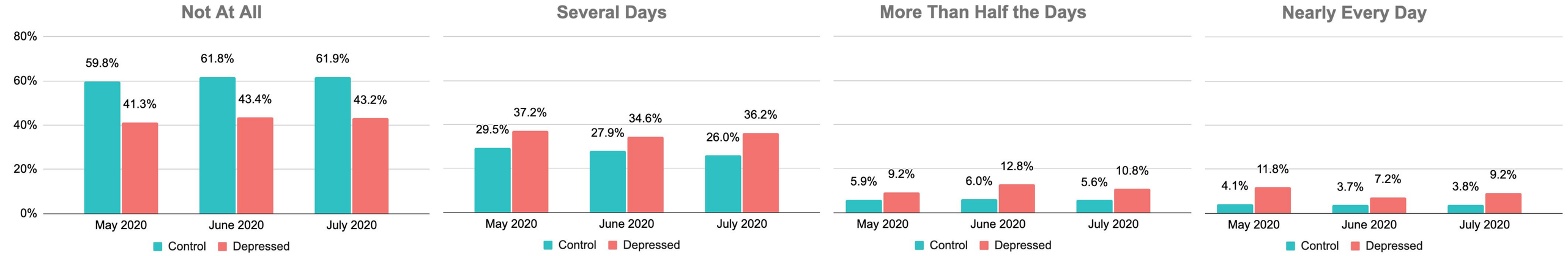
<u>70% from groups that are historically underrepresented in biomedical research</u>

February COPE Results: ***When a COVID-19 vaccine is available, how likely are you to want to receive vaccination?***

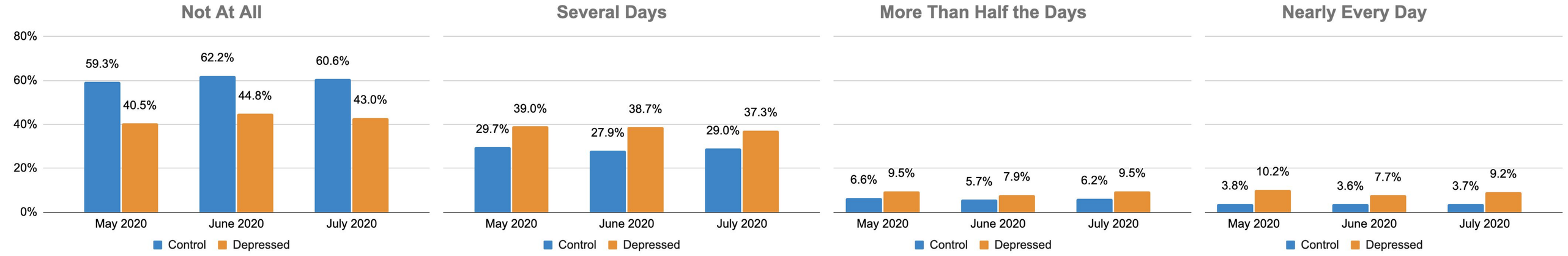


Demonstration Project: Mental Health during COVID-19 of Participants with Depression

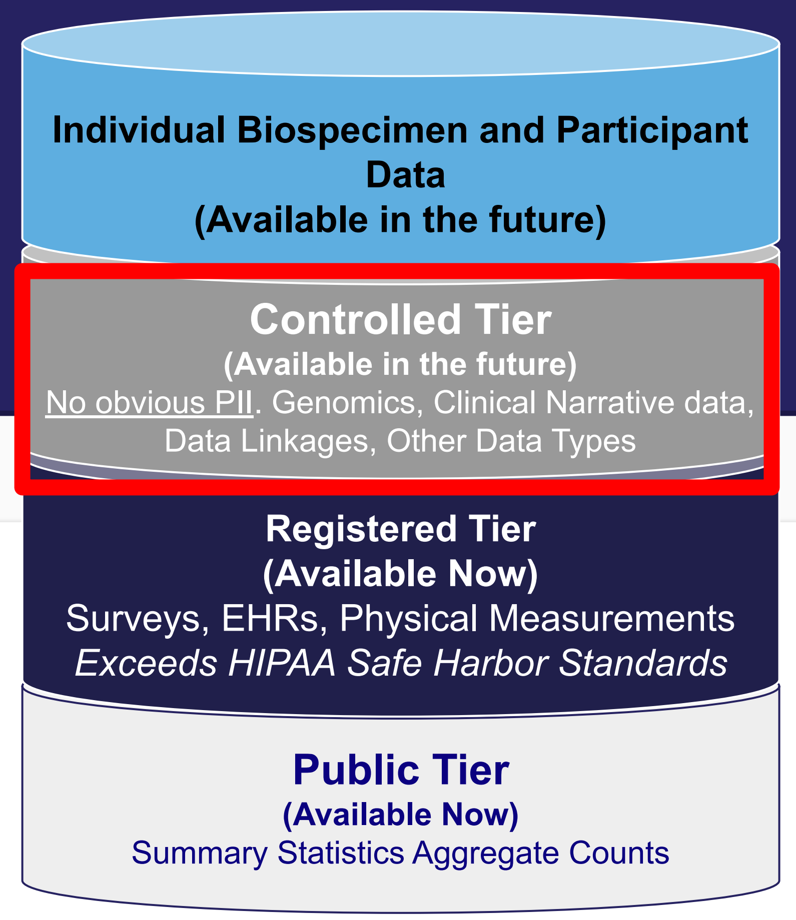
In the past 2 weeks, how often have you been bothered by feeling down, depressed or hopeless?



In the past 2 weeks, how often have you been bothered by little interest or pleasure in doing things?

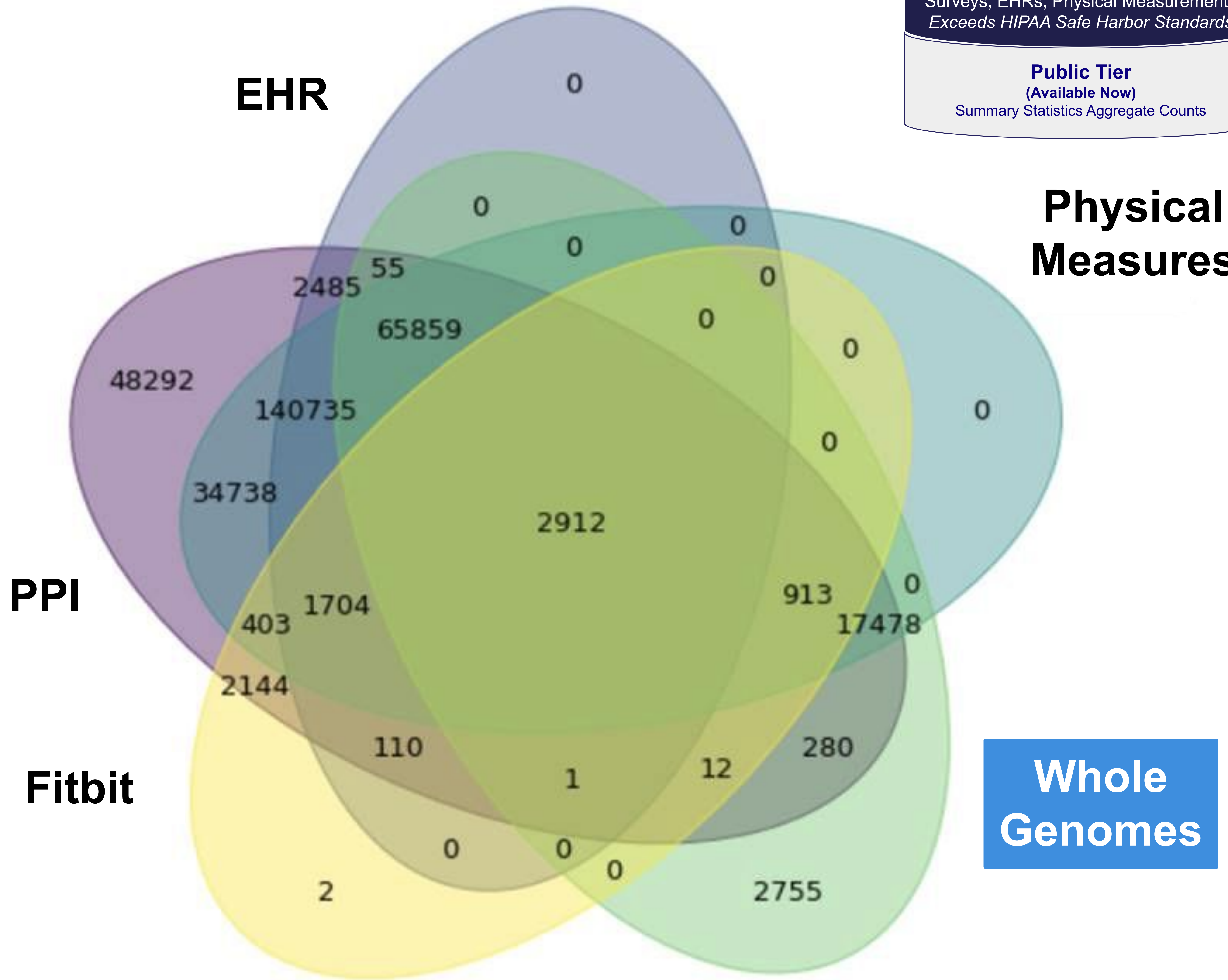


Upcoming Controlled Tier + Genomics Data Release



Coming <u>Winter 2021/2022</u>

- Expected 90,000 WGS + 130,000 arrays
- More participants
- COVID diagnoses and surveys
- More detailed demographic data
- More Fitbit data



Thank You!

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