The *All of Us* Research Program Experience

All of Us RESEARCH PROGRAM

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University of Pittsburgh School of Pharmacy

All of Us Pennsylvania; Co-Chair, PGx, *All of Us* Genome Centers

No conflicts to disclose

NIH National Institutes of Health

University of Pittsburgh School of Pharmacy

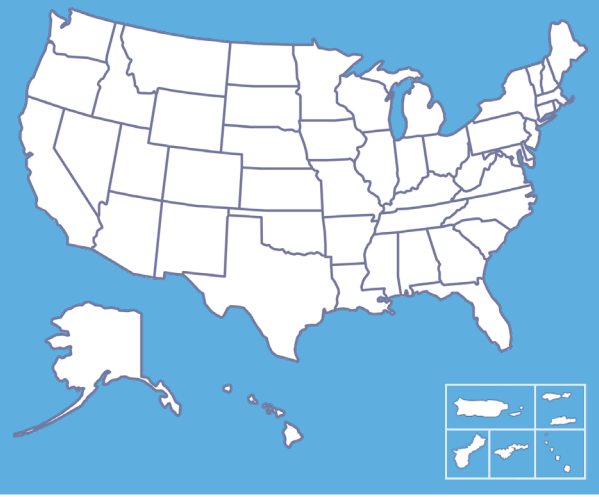
#JoinAllofUs

One of the world's largest, most diverse biomedical datasets

Inviting

1 Million

or more people from across the United States



Data available from **413,450+** participants

75%

identify with communities underrepresented in biomedical research

45%

are from racial and ethnic minority groups

Data as of April 2023

Why return genetic information?

- **Genetic information can be useful and engaging**
  - **Important health information**: medication response and hereditary disease risk
  - National academies, ASHG, ACMG, ESHG have emphasized in importance of return of results and engaged the question of opportunistically using data streams to identify individuals at high risk of penetrant, treatable disorders.
  - 26+ million people have purchased at-home genetic tests.

- **A longitudinally-engaged population increases the value of the program**
  - The promise of returned information **encourages recruitment** into the study.
  - Ongoing engagement **drives retention and long-term participation**.
  - Participants see the progress of the program in very personal ways, which **drives understanding of and advocacy for the program**.

Return of Results ↔ Return of value

Why does *All of Us* focus on PGx?

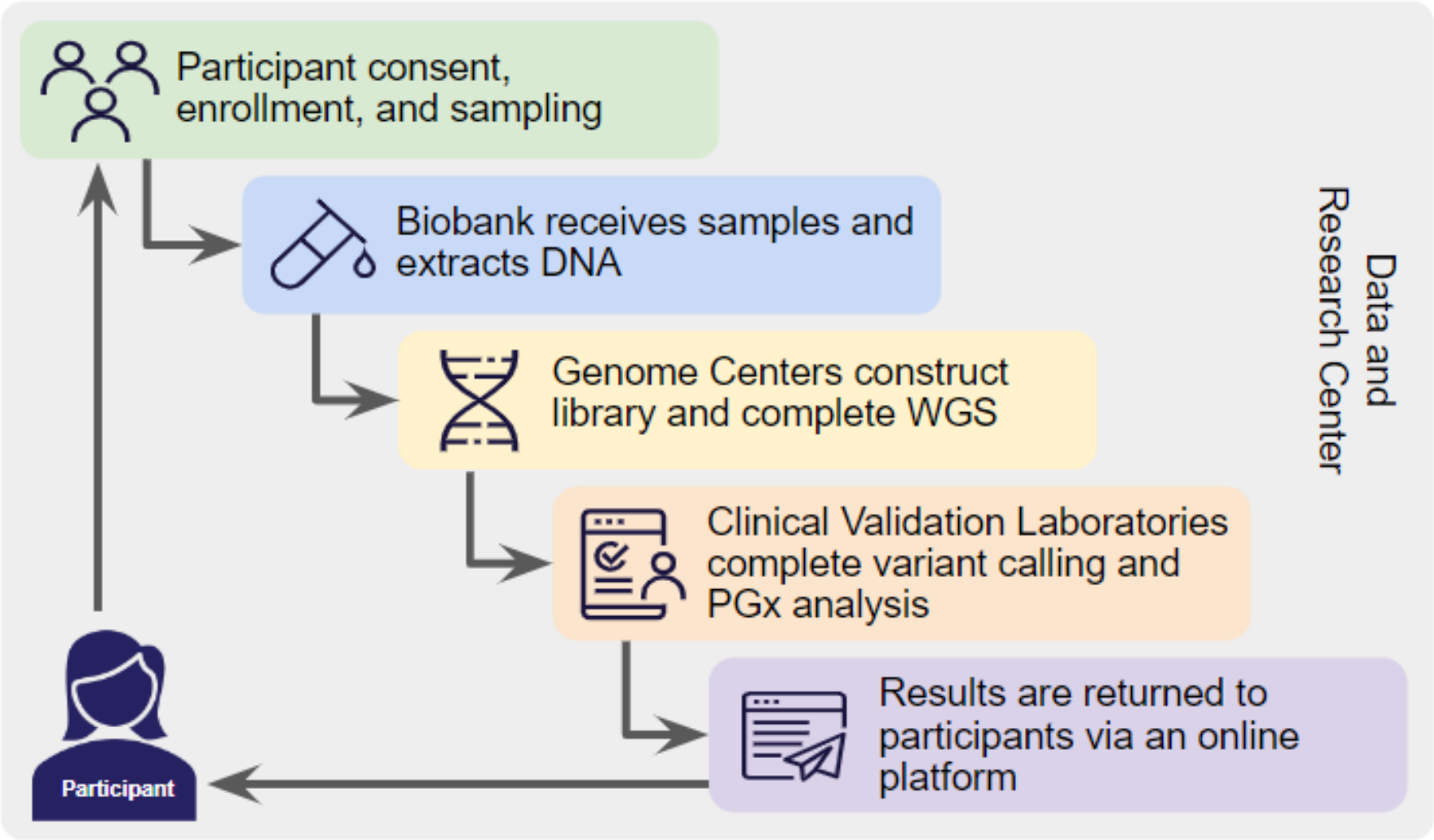
- Variability in medication response is widely understood
- Strong scientific evidence for impact on outcomes
- Testing is feasible and has life-long value
- Variants are common; most participants are expected to carry at least one variant
- Already implemented in clinical practice

PGx data were ranked as highly valuable by participants

Wilkins, AoU Return of Results conf, 3/2017

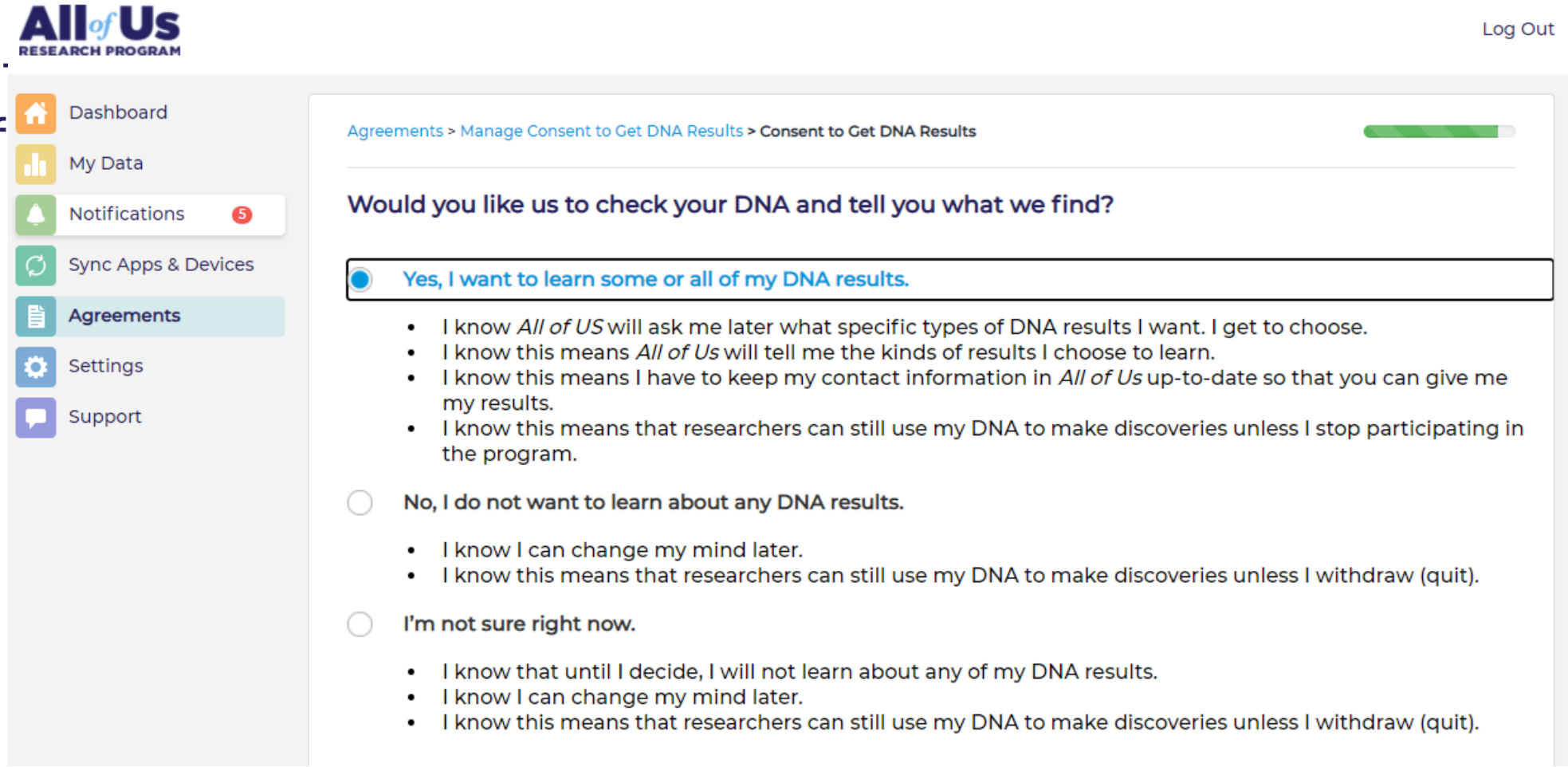
AoU program design

Participant-centered model with return of genomic results from WGS



Return of results consent model

- Participants elect for genomics return to receive results; can then choose what is returned.
- Posi
  conf
- PGx



All of Us regulatory oversight

National Institutes of Health

Study sponsor

Institutional Review Board (IRB)

Ensuring that the rights and welfare of research participants are overseen and protected uniformly

Charged with reviewing the protocol, informed consent, and other **participant-facing materials**

Representatives with diverse backgrounds, expertise, and perspectives

Food and Drug Administration (FDA)

Responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, **medical devices**, our nation's food supply, cosmetics, and products that emit radiation

Office of In Vitro Diagnostics and Radiological Health, Office of Product Evaluation and Quality

Investigational Device Exemption (IDE): **consent to return of health-related results**

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CLIA standards, but not a clinical test

Clinical Standards (CLIA)

- **Sample collection** meets CLIA/CAP standards.
- **Primary data** generation is at CLIA-certified Genome Centers (WGS).
- **Interpretation and secondary confirmation** of positive results is at CLIA-certified Clinical Validation Laboratories.

Research data is not a clinical test

- There is **no supervising physician**
- There is **no clinical test requisition**
- Sample handling logistics are complex

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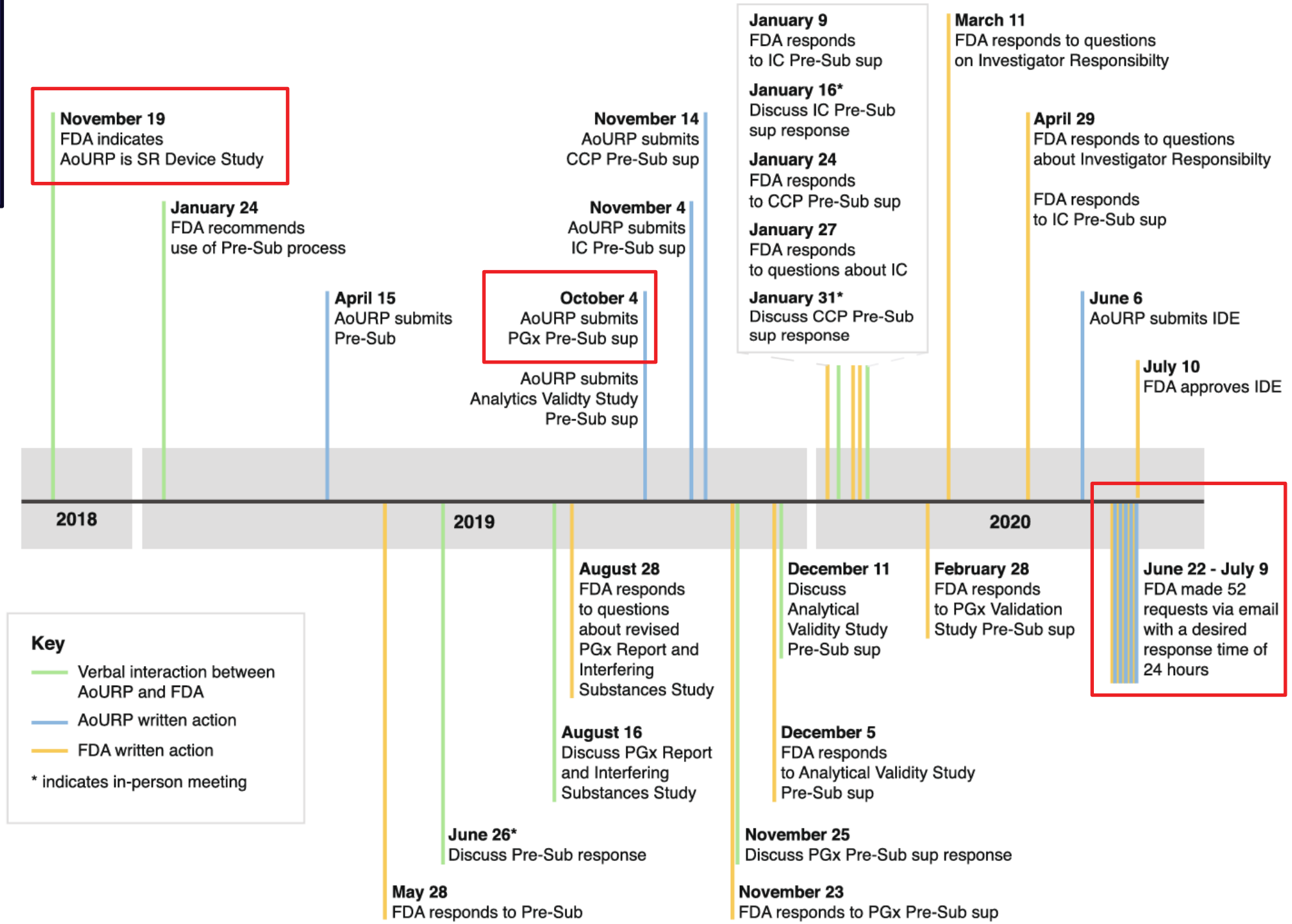
IDE process & timeline

~19 months



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Lessons learned

- There was no clear predicate device; “Device” included whole process
- FDA strongly preferred patient-derived clinical specimens over reference samples derived from cell lines as “ground truth”.
- FDA required us to demonstrate performance in every reportable gene and PGx allele.
- Research results are deemed from an investigational device and cannot be used to direct clinical care

Guiding principles of gene selection

AoU Genomics committee (2018) and PGx Workgroup

- Focused on participant value and actionability
- Emphasis on gene-drug associations with the highest level of evidence
- Included genes impacting drug efficacy and adverse reaction potential
- Considers testing methods and AoU return of results model

Pharmacogenes for initial return	
CYP2C19	**Cytochrome p450 2C19**
DPYD	**Dihydropyrimidine dehydrogenase**
G6PD	**Glucose-6-phosphate dehydrogenase**
NUDT15	**Nudix hydrolase 15**
SLCO1B1	**Organic anion transporting polypeptide 1B1**
TPMT	**Thiopurine methyltransferase**
UGT1A1	**UDP Glucuronosyltransferase 1A1**

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Rigor of allele/variant selection

Evidence review criteria

1. Selection of alleles with known functional consequence
2. Consideration of clinical testing “standards”
   - Tier 1 and Tier 2 AMP recommendations when available
   - coverage by leading institutional/lab tests.
3. Identification of core variants necessary to call alleles per PharmVar
4. No absolute frequency cut-offs. Consideration of rare alleles that are specific to ethnic groups.
5. Filtered for targets with available controls

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CPIC® Clinical Pharmacogenetics Implementation Consortium

PG KB PHARMGKB

PharmVar Pharmacogene Variation Consortium

Analytical validation

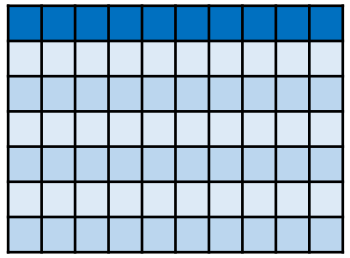
- Each genome center needed to achieve FDA IDE standards
- Completed a priori validation of PGx targets (desired variants when controls exist)
- **Accuracy of PGx calling**:
  - Blood-derived clinical samples (n= 159; orthogonally validated) = **100% concordance**
  - For rare alleles/no clinical controls: Get-RM cell lines (n = 135) = **99.8% concordance**
  - For those not in Get-RM, 1000 Genomes cell lines (n = 29) = **100% concordance**
- **Inter- and intra-lab equivalence >99%**
- **Precision of AoU PGx calling = 99.3%**

Variant/alleles

Gene	Alleles/variants
CYP2C19	*2,*3,*4,*6,*8,*9,*10,*16,*17,*22, *24,*35
DPYD	c.1905+1G>A (*2), c.1129-5923C>G, c.1679T>G (*13), c.2846A>T
G6PD	A-202A_376G; A-968C_376G; Asahi; Aures; Canton, Taiwan-Hakka, Gifu-like, Agrigento-like; Chinese-5; Ilesha; Kaiping, Anant, Dhon, Sapporo-like, Wosera; Kambos; Kalyan-Kerala, Jamnaga, Rohini; Mediterranean, Dallas, Panama, Sassari, Cagliari, Birmingham; Quing Yuan, Chinese-4; Seattle, Lodi, Modena, Ferrara II, Athens-like; Sibari; Ube Konan; Union, Maewo, Chinese-2, Kalo; Viangchan, Jammu
NUDT15	*2, *3
SLCO1B1	*5,*15,*17
TPMT	*2,*3A,*3B,*3C
UGT1A1	*6,*27,*28,*36,*37

Interpretative pipelines

Variants



Star allele “diplotype”

*1/*2

Predicted phenotype

CYP2C19
Intermediate Metabolizer

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CPIC®
Clinical Pharmacogenetics Implementation Consortium

Reporting drug associations

- Guiding principle: *Including drug information provides value*
- Each association with predicted phenotype evaluated
- Considers medication factors such as route of administration
- Achieved through highly iterative discussions with FDA (CDRH/CDER)

"For a medication to be listed, a gene-phenotype-drug combination must (1) appear in FDA-approved drug product labeling (minimally in the Boxed Warning, Dosage and Administration, Contraindications, or Indications sections), (2) appear in the FDA Table of Pharmacogenetic Associations (Section A: Data support therapeutic management recommendations or Section B: Data Indicate a Potential Impact on Safety or Responses), OR (3) have a recommendation for alternative medication or dosing modification within a CPIC guideline."

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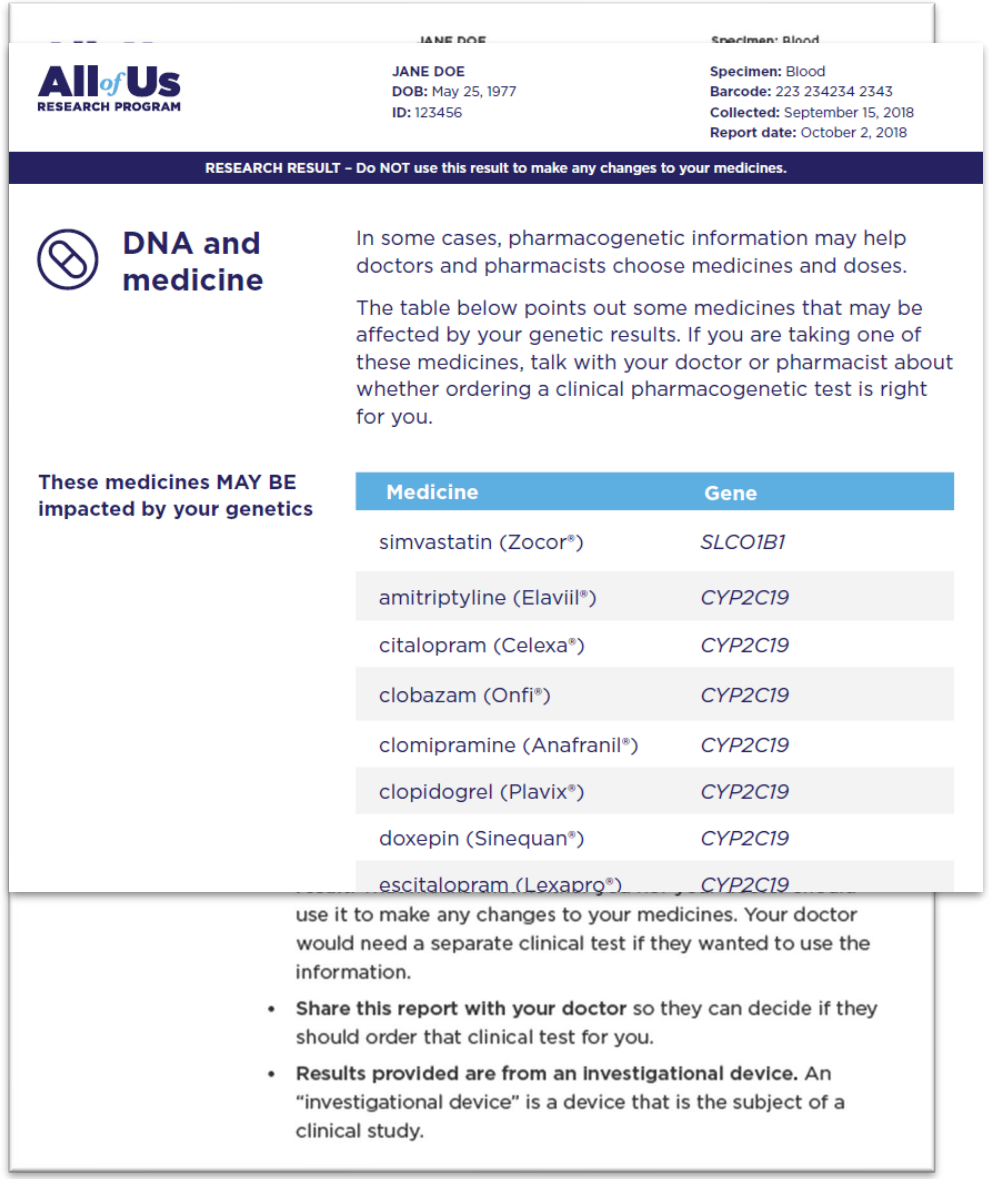
“Medicine and Your DNA” report

- Goal is to inform, engage, and achieve high user comprehension
- Help participants self-identify as a person who should consider clinical PGx testing
- Investigational device, “Research result”
- “If your doctor has prescribed medicine for you, keep taking it”
- Encourages sharing and discussion with physician and pharmacist
- Includes normal results
- Genetic information is just one piece



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 – Do NOT use this result to make any changes to your medicines.

DNA and medicine

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

The table below 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.

These medicines MAY BE impacted by your genetics

Medicine	Gene
simvastatin (Zocor®)	*SLCO1B1*
amitriptyline (Elavil®)	*CYP2C19*
citalopram (Celexa®)	*CYP2C19*
clobazam (Onfi®)	*CYP2C19*
clomipramine (Anafranil®)	*CYP2C19*
clopidogrel (Plavix®)	*CYP2C19*
doxepin (Sinequan®)	*CYP2C19*
escitalopram (Lexapro®)	*CYP2C19*

use it to make any changes to your medicines. Your doctor would need a separate clinical test if they wanted to use the information.

- **Share this report with your doctor** so they can decide if they should order that clinical test for you.
- **Results provided are from an investigational device.** An “investigational device” is a device that is the subject of a clinical study.

Program status

First returns in Fall 2022; over 225k have been notified to date

Potential content updates

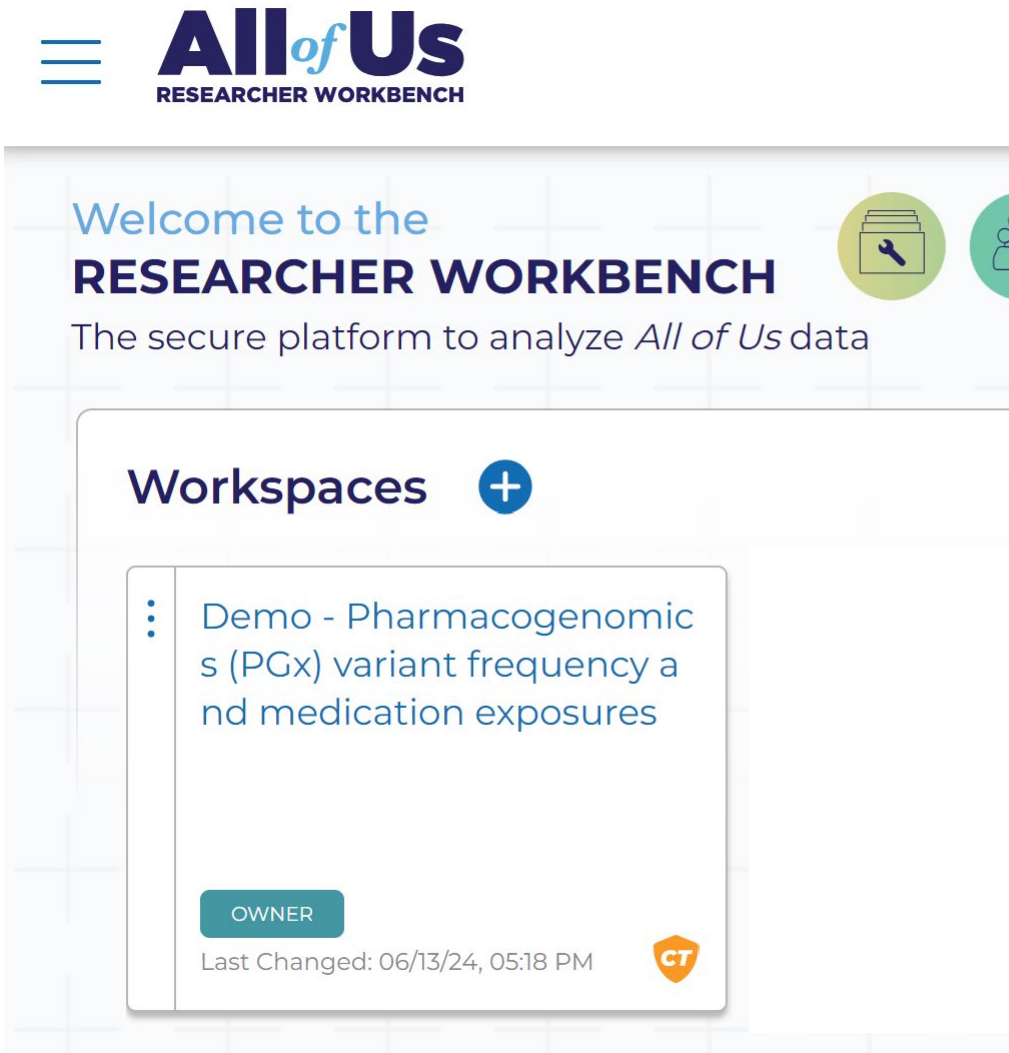
- Expanded genes and allele validations as controls are identified
- Incorporation of new guidelines and FDA revisions as knowledge grows
- Inclusion of planned PGx targets with structural variation (e.g. *CYP2D6*)
- As we learn more from RoR model

Take-aways

- Returning personal results from research data **drives program goals.** **PGx** is one of the most commonly requested types of information
- Returning this information is **regulated** by IRB & FDA.
- Over **225,000** participants have received offer for their PGx report
- The information **cannot be used** to guide clinical care. Goal is to help participants **self-identify** as a person who should discuss clinical PGx testing with their clinicians
- **Clarity is important**, some common phrases are often misunderstood

PGx haplotypes are now available for researchers!

- Featured workspace in Researcher Workbench includes PGx frequencies and medication exposures
- PGx haplotypes (15 genes) for with 245k diverse participants using srWGS (v7 cohort) using Stargazer and PharmCAT
- Training workshop at PGRN meeting in Sept!



AoURP has an FDA IDE to return PGx

- Validated to FDA standards
- Targets with the highest level of evidence, participant value, and actionability.

Pharmacogenes in initial return

CYP2C19	Cytochrome p450 2C19
DPYD	Dihydropyrimidine dehydrogenase
G6PD	Glucose-6-phosphate dehydrogenase
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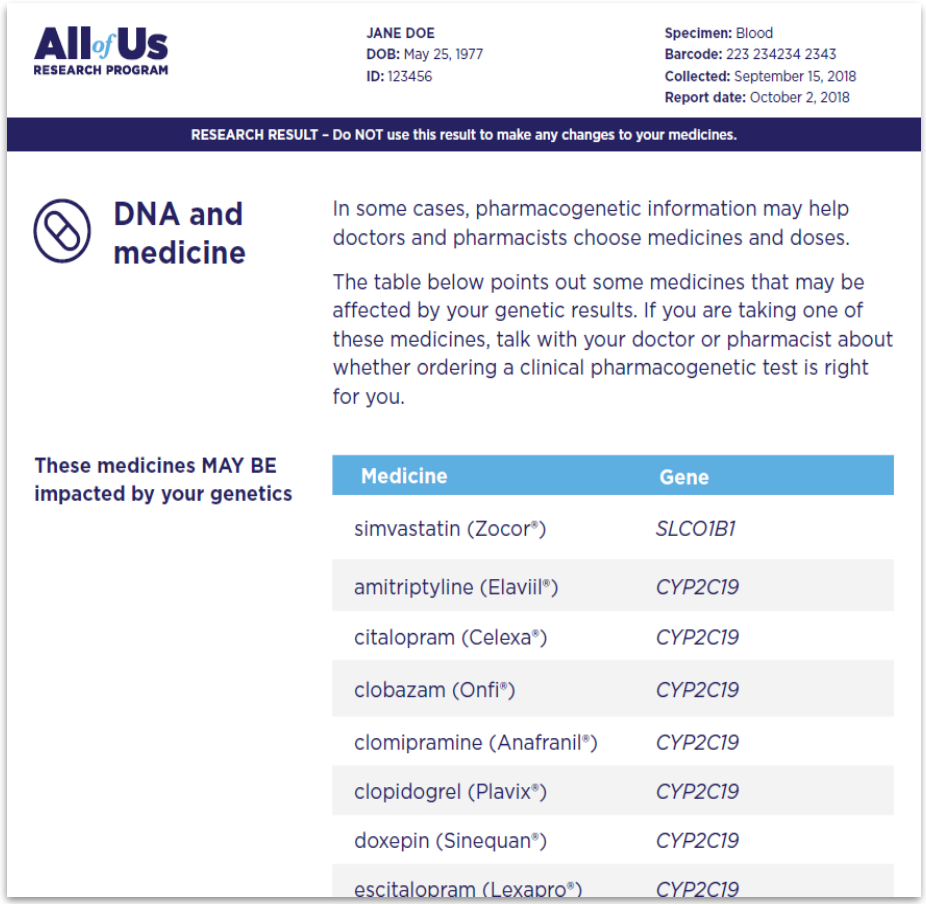

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clopidogrel (Plavix®)	*CYP2C19*
doxepin (Sinequan®)	*CYP2C19*
escitalopram (Lexapro®)	*CYP2C19*

What is the *All of Us Research Program*?

Nurture relationships

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

Our mission

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

Deliver the largest, richest biomedical dataset

that is easy, safe, and free to access

Catalyze a robust ecosystem

of researchers and funders hungry to use and support it

AoU collects a wide range of different data types

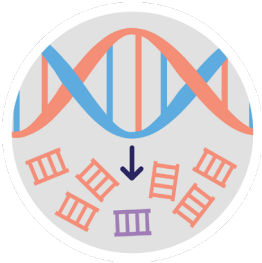
The *All of Us* curates a range of different data types as part of the data collection process.

413,350+
Survey Responses

337,500+
Physical Measurements

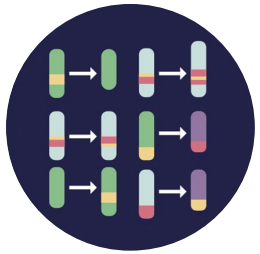
312,900+
Genotyping Arrays

287,000+
Electronic Health Records



245,350+
Whole Genome Sequences (WGS)

15,600+
Fitbit Records



11,350+
Structural Variants

1,000+
Long-Read Sequences

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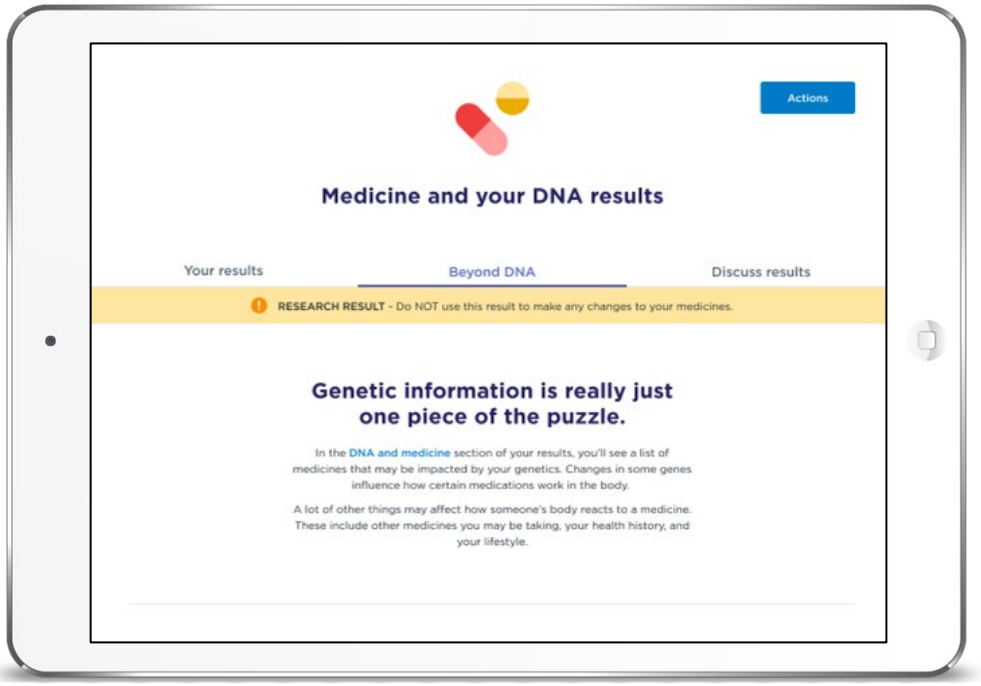
Data as of April 2023 Curated Data Repository (CDR) v7 data release and CDRv7 off-cycle release in April 2024

Key cautions in the Medicine and your DNA Report

- Do not make any changes to your medicine from these results.
- A lot of things (other than DNA) affect how someone's body reacts to a medicine.
- These are research results.
- The results are from an investigational device.



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 genetics 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 device.** An "investigational device" is a device that is the subject of a clinical study.

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“Medicine and Your DNA” report user comprehension

97.6%

Comprehension of genetic knowledge

(i.e. “My DNA may impact how I respond to certain medicines.”)

98.4%

comprehension of self-efficacy concepts

(i.e. “I understand I should not change my medical care based on my DNA test results.”)

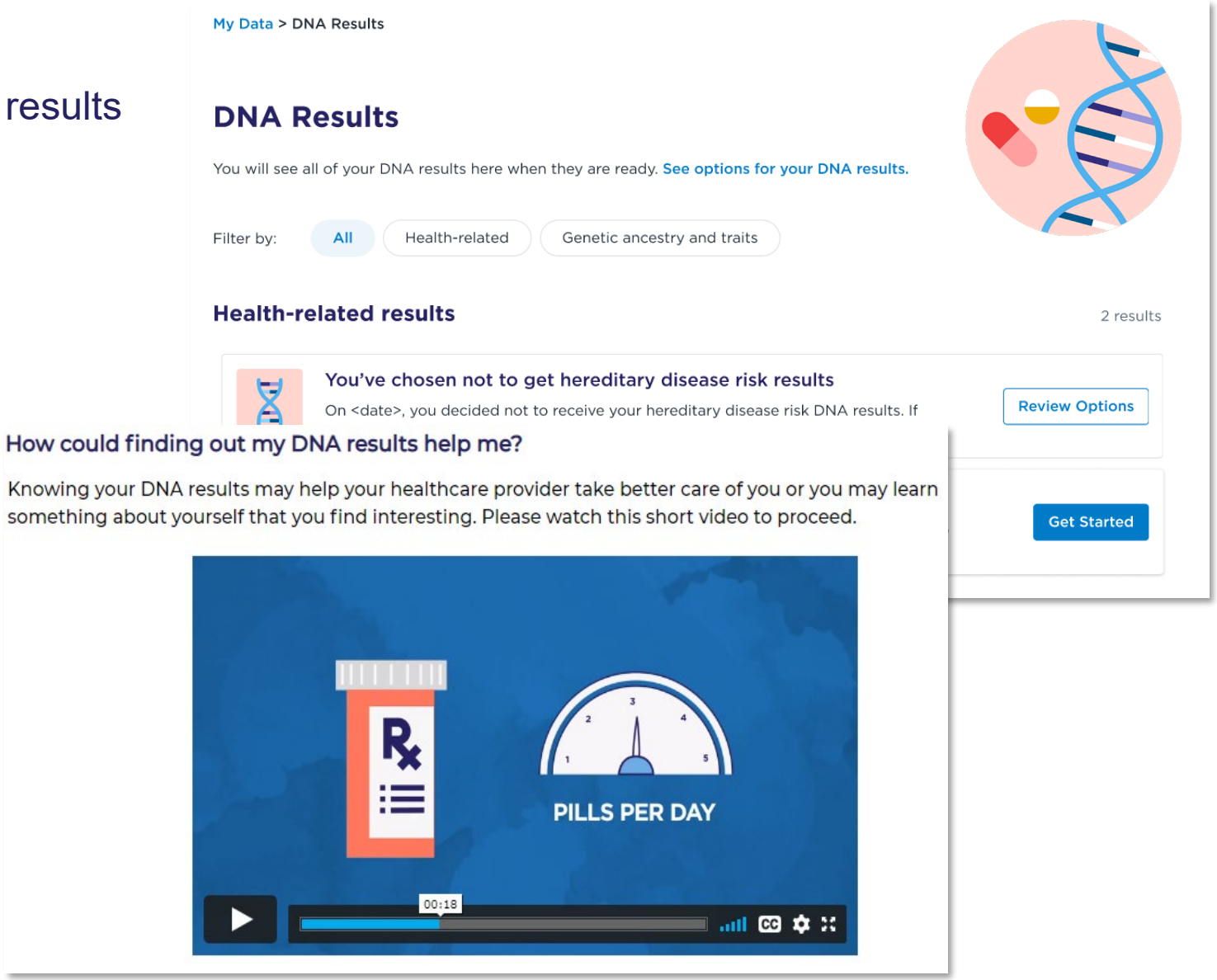
Some key lessons learned regarding language:

Participant access to their “Medicine and Your DNA” report

Return of results steps:

1. Notification that AoU is ready to generate results
2. Complete informing loops
3. Generate results
4. Receive results

Genetic counseling can be accessed for free (not required)



Participant experience walkthrough

Medicine and your DNA results

Your results | Beyond DNA | Discuss results

Before we get to your results, here is some helpful information about genes and medicine.

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.”

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.

Result sections

Beyond DNA

Discuss results

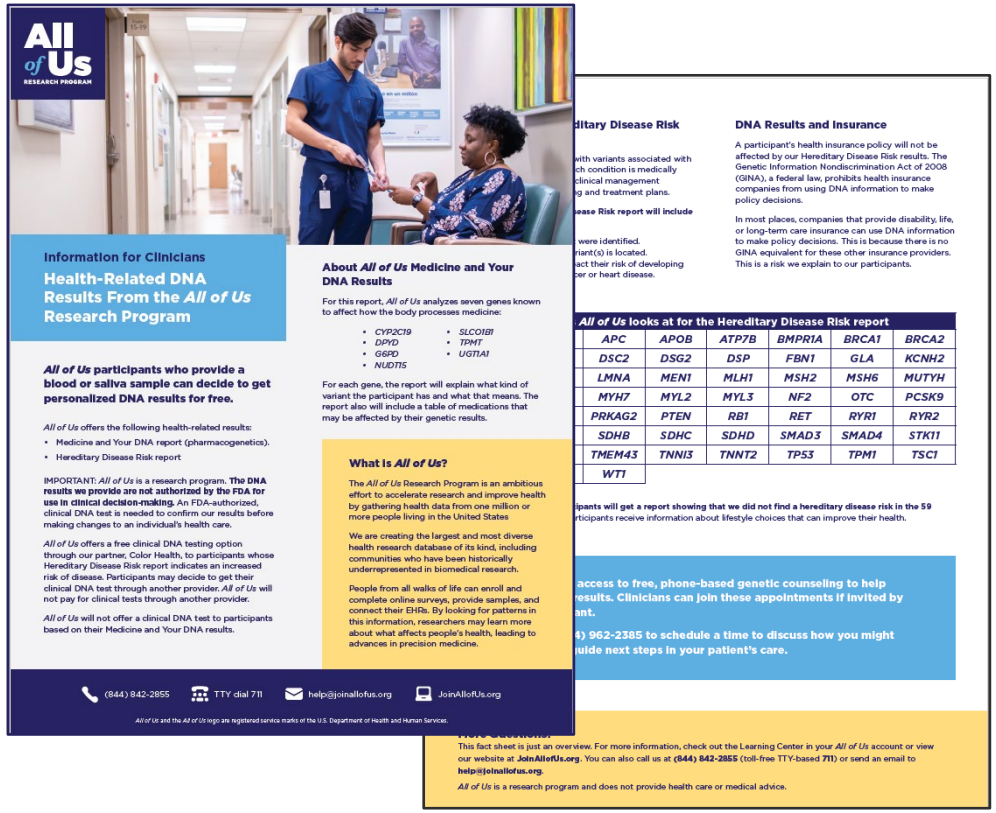
Download

Report PDF

Information sheet for doctors

Participants can download a copy of their report by scrolling to the bottom of the page.

Health care provider-facing materials



All of Us RESEARCH PROGRAM

Information for Clinicians

Health-Related DNA Results From the *All of Us* Research Program

***All of Us* participants who provide a blood or saliva sample can decide to get personalized DNA results for free.**

All of Us offers the following health-related results:

- Medicine and Your DNA report (pharmacogenetics).
- Hereditary Disease Risk report

IMPORTANT: *All of Us* is a research program. **The DNA results we provide are not authorized by the FDA for use in clinical decision-making.** An FDA-authorized, clinical DNA test is needed to confirm our results before making changes to an individual's health care.

All of Us offers a free clinical DNA testing option through our partner, Color Health, to participants whose Hereditary Disease Risk report indicates an increased risk of disease. Participants may decide to get their clinical DNA test through another provider. *All of Us* will not pay for clinical tests through another provider.

All of Us will not offer a clinical DNA test to participants based on their Medicine and Your DNA results.

About *All of Us* Medicine and Your DNA Results

For this report, *All of Us* analyzes seven genes known to affect how the body processes medicine:

- *CYP2C19*
- *DPYD*
- *G6PD*
- *NUDT15*
- *SLCO1B1*
- *TPMT*
- *UGT1A1*

For each gene, the report will explain what kind of variant the participant has and what that means. The report also will include a table of medications that may be affected by their genetic results.

What is *All of Us*?

The *All of Us* Research Program is an ambitious effort to accelerate research and improve health by gathering health data from one million or more people living in the United States

We are creating the largest and most diverse health research database of its kind, including communities who have been historically underrepresented in biomedical research.

People from all walks of life can enroll and complete online surveys, provide samples, and connect their EHRs. By looking for patterns in this information, researchers may learn more about what affects people's health, leading to advances in precision medicine.

(844) 842-2855 TTY dial 711 help@joinallofus.org JoinAllofUs.org

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ditary Disease Risk

with variants associated with
ch condition is medically
clinical management
g and treatment plans.

ease Risk report will include

were identified.
riant(s) is located.
act their risk of developing
er or heart disease.

DNA Results and Insurance

A participant's health insurance policy will not be affected by our Hereditary Disease Risk results. The Genetic Information Nondiscrimination Act of 2008 (GINA), a federal law, prohibits health insurance companies from using DNA information to make policy decisions.

In most places, companies that provide disability, life, or long-term care insurance can use DNA information to make policy decisions. This is because there is no GINA equivalent for these other insurance providers. This is a risk we explain to our participants.

***All of Us* looks at for the Hereditary Disease Risk report**

	APC	*APOB*	*ATP7B*	*BMPR1A*	*BRCA1*	*BRCA2*
	DSC2	*DSG2*	*DSP*	*FBN1*	*GLA*	*KCNH2*
	LMNA	*MEN1*	*MLH1*	*MSH2*	*MSH6*	*MUTYH*
	MYH7	*MYL2*	*MYL3*	*NF2*	*OTC*	*PCSK9*
	PRKAG2	*PTEN*	*RB1*	*RET*	*RYR1*	*RYR2*
	SDHB	*SDHC*	*SDHD*	*SMAD3*	*SMAD4*	*STK11*
	TMEM43	*TNNI3*	*TNNT2*	*TP53*	*TPM1*	*TSC1*
	WT1					

ipants will get a report showing that we did not find a hereditary disease risk in the 59
rticipants receive information about lifestyle choices that can improve their health.

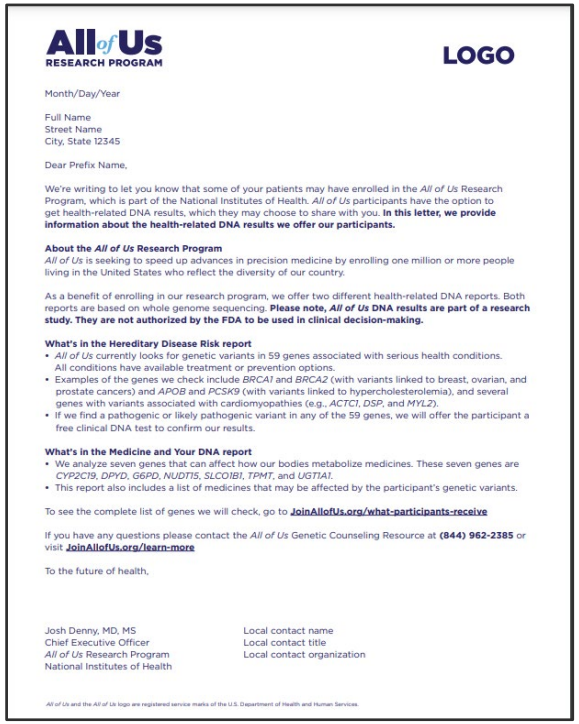
access to free, phone-based genetic counseling to help
esults. Clinicians can join these appointments if invited by
ant.

4) 962-2385 to schedule a time to discuss how you might
lude next steps in your patient's care.

This fact sheet is just an overview. For more information, check out the Learning Center in your *All of Us* account or view our website at **JoinAllofUs.org**. You can also call us at **(844) 842-2855** (toll-free TTY-based **711**) or send an email to **help@joinallofus.org**.

All of Us is a research program and does not provide health care or medical advice.

Information for Clinicians Factsheet: This factsheet gives HCPs an overview of what their patients may receive in their health-related genetic results reports and information about how to use these results.



All of Us RESEARCH PROGRAM

LOGO

Month/Day/Year

Full Name
Street Name
City, State 12345

Dear Prefix Name,

We're writing to let you know that some of your patients may have enrolled in the *All of Us* Research Program, which is part of the National Institutes of Health. *All of Us* participants have the option to get health-related DNA results, which they may choose to share with you. **In this letter, we provide information about the health-related DNA results we offer our participants.**

About the *All of Us* Research Program

All of Us is seeking to speed up advances in precision medicine by enrolling one million or more people living in the United States who reflect the diversity of our country.

As a benefit of enrolling in our research program, we offer two different health-related DNA reports. Both reports are based on whole genome sequencing. **Please note, *All of Us* DNA results are part of a research study. They are not authorized by the FDA to be used in clinical decision-making.**

What's in the Hereditary Disease Risk report

- *All of Us* currently looks for genetic variants in 59 genes associated with serious health conditions. All conditions have available treatment or prevention options.
- Examples of the genes we check include *BRCA1* and *BRCA2* (with variants linked to breast, ovarian, and prostate cancers) and *APOB* and *PCSK9* (with variants linked to hypercholesterolemia), and several genes with variants associated with cardiomyopathies (e.g., *ACTC1*, *DSP*, and *MYL2*).
- If we find a pathogenic or likely pathogenic variant in any of the 59 genes, we will offer the participant a free clinical DNA test to confirm our results.

What's in the Medicine and Your DNA report

- We analyze seven genes that can affect how our bodies metabolize medicines. These seven genes are *CYP2C19*, *DPYD*, *G6PD*, *NUDT15*, *SLCO1B1*, *TPMT*, and *UGT1A1*.
- This report also includes a list of medicines that may be affected by the participant's genetic variants.

To see the complete list of genes we will check, go to **JoinAllofUs.org/what-participants-receive**

If you have any questions please contact the *All of Us* Genetic Counseling Resource at **(844) 962-2385** or visit **JoinAllofUs.org/learn-more**

To the future of health,

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

Local contact name
Local contact title
Local contact organization

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HCP Distribution Letter: This letter informs HCPs that one of their patients may be getting health-related results from AoU. It provides a brief overview of the AoU Research Program and what participants receive in the Hereditary Disease Risk report and Medicine and Your DNA report.