Pharmacogenomics Return of Results in the All of Us Research Program

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Image credit: NHGRI Genome.gov

Key features of the *All of Us* Research Program

- Participant-centered model for return of genomic results
- Needs to meet regulatory requirements
- Challenge of scaling to 1M participants
- Focus on diversity

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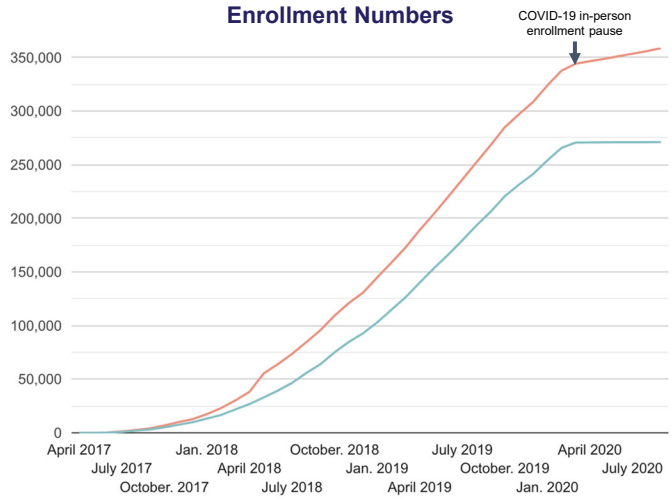
Status of the Program (10/25/20)

360,000+
Participants

230,000+
Electronic Health Records

271,000+
Participants who have completed initial steps of the program

277,000+
Biosamples



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

Slide by Josh Denny

Why Focus on Pharmacogenomics?

- Participants expect return of PGx results
- Return of results → Return of value
- In the *All of Us* Research Program 77 community studios (n=654):

PGx data were ranked as most valuable to participants
(more than results about the genetic risk of disease)

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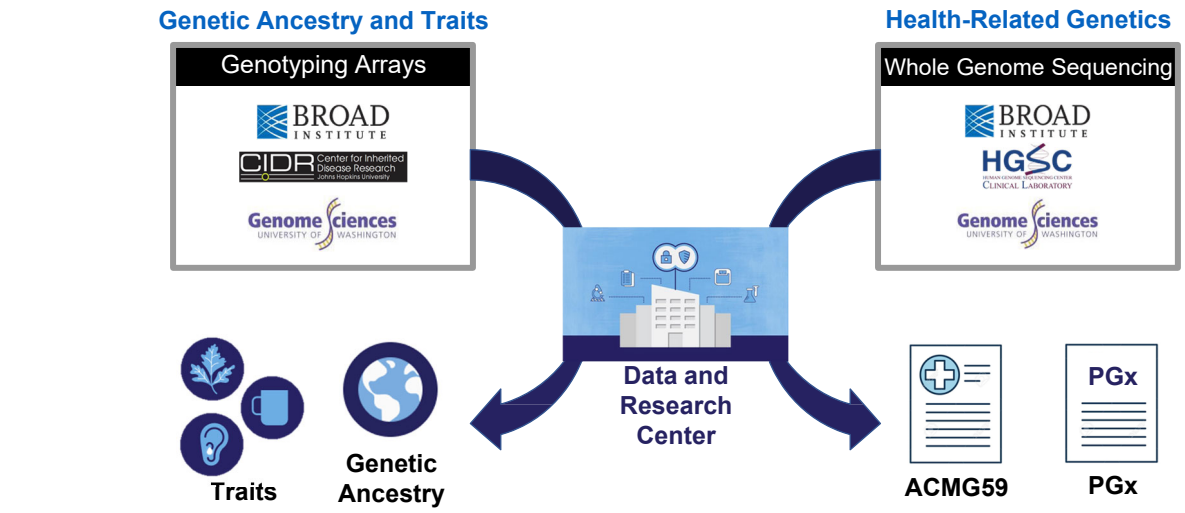
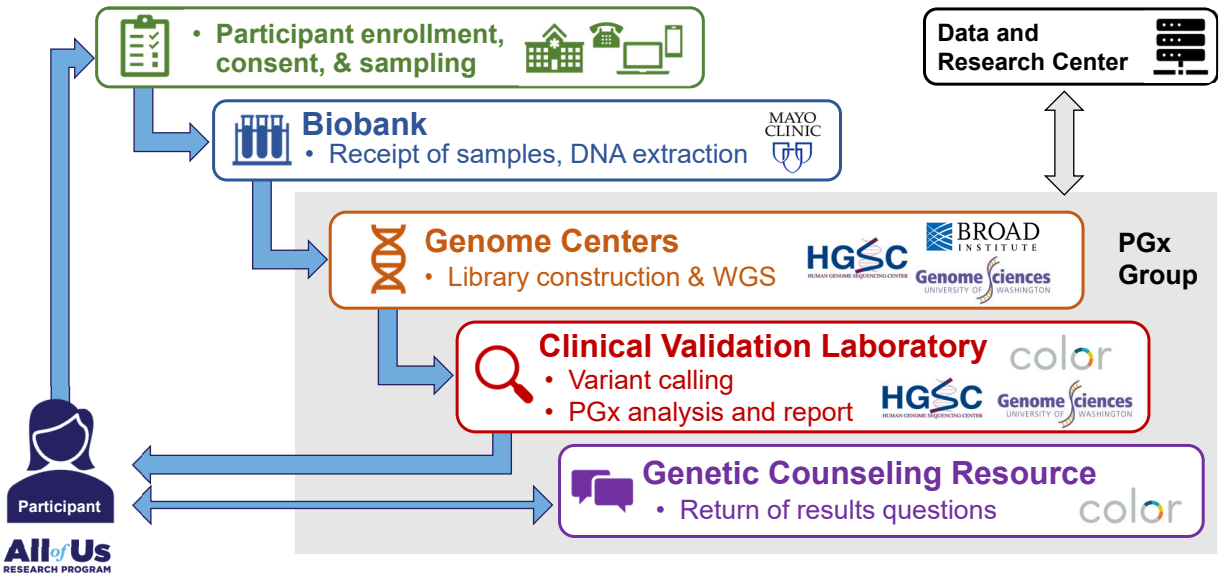
Wilkins, AoU Return of Results conf, 3/2017

Returning Value to Participants: Genetic Return of Results



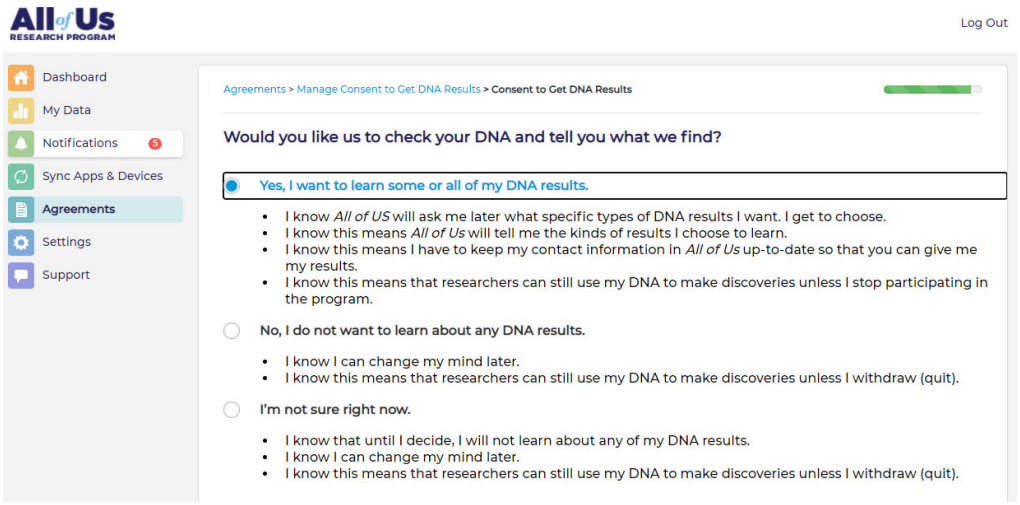
Slide by Josh Denny

PGx Testing at *All of Us* Genome Centers



Consent model

- Participants must agree to genomics return



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Regulatory approval

- Investigational Device Exemption (IDE) required from the FDA
- Allows the return of certain findings from the investigational device to participants
- AoU works closely with the FDA to enable PGx return of results safely and supported by the highest level of evidence.
- IDE submission was refined through a series of pre-submissions and responses, in-person meetings, and teleconferences over a period of 18 months

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FDA U.S. FOOD & DRUG ADMINISTRATION

Guiding principles of gene selection

AoU Genomics committee (2018) and PGx Workgroup

- Focused on participant value and actionability
- Emphasis on gene-drug associations with undisputable evidence
- Included genes impacting drug efficacy and adverse reaction potential
- Consideration of 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

CPIC Clinical Pharmacogenetics Implementation Consortium

PharmVar Pharmacogene Variation Consortium

1. Selection of alleles with known functional consequence
2. Consideration clinical testing “standards”
   - Tier 1 and Tier 2 AMP recommendations when available
   - Common 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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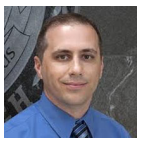
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BCM-HGSC


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BCM-HGSC

Analytical Validation

- Each genome center needed to achieve FDA IDE standards
- Completed a priori validation (all targeted desired variants when controls exist)
- **Accuracy of PGx calling** was determined using:
  - Blood-derived real clinical samples (n= 159; previous orthogonally validated) = **100% concordance**
  - For rare alleles or if 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 AoUPGx calling = 99.3%**

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Variant/allele selection

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

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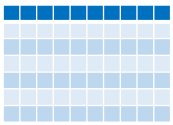
Interpretation

Variants → **Star allele "diplotype"** → **Predicted phenotype**



*1/*2

***CYP2C19* Intermediate Metabolizer**

CPIC® Clinical Pharmacogenetics Implementation Consortium

- Translation translation tables
- Standardized phenotype terms (when available)

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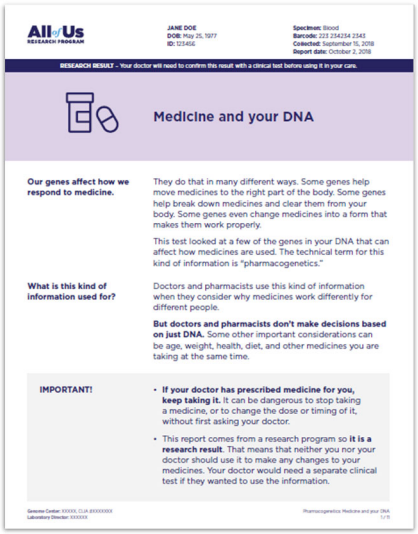
"Medicine and Your DNA" report design

- Goal is to inform, engage, and achieve high user comprehension
- Investigational device, "Research result"
- "If your doctor has prescribed medicine for you, keep taking it"
- Encourages sharing with the participant's doctor and pharmacist.
- Includes normal results
- Emphasizes genetic information is just one piece of the puzzle



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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.
- This report comes from a research program so **it is a research result**. That means that neither you nor your doctor should use it to make any changes to your medicines. Your doctor would need a separate clinical test if they wanted to use the information.

Genome Center: XXXXX, CLIA #XXXXXXX
Laboratory Director: XXXXXX

Pharmacogenetics Medicine and your DNA
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Reporting Drug Associations

- Guiding principle: *"Including drug information provides value"*
- Based on rigorous evidence review using
  - CPIC guidelines/supplements
  - FDA labels and Table of PGx Associations
  - Primary literature
- Considering medication factors such as route of administration
- Highly collaborative/iterative with FDA (CDRH/CDER)

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Reportable associations

Gene	Drug(s)
CYP2C19	amitriptyline (Elavil®), brivaracetam (Briviact®), citalopram (Celexa®), clobazam (Onfi®), clomipramine (Anafranil®), clopidogrel (Plavix®), doxepin (Sinequan®), escitalopram (Lexapro®), flibanserin (Addyi®), imipramine (Tofranil®), pantoprazole (Protonix®), setraline (Zoloft®), trimipramine (Surmontil®), voriconazole (Vfend®)
DPYD	capecitabine (Xeloda®), fluorouracil (Adrucil®)
TPMT/NUDT15	azathioprine (Imuran®), mercaptopurine (Purinethol®) thioguanine
SLCO1B1	simvastatin (Zocor®)
UGT1A1	atazanavir (Reyataz®), belinostat (Beleodaq®), Irinotecan (Camptosar®)

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Reportable associations

Gene	Drug(s)
G6PD	chloramphenicol, dabrafenib (Tafinlar®), dapsone, hydroxychloroquine (Plaquenil®), local anesthetics, mafenide (Sulfamylon®), methylene blue, nalidixic acid (NegGram®), nitrofurantoin (Macrobid®, Macrodantin®, Furadentin®), pegloticase (Krystexxa®), phenazopyridine, primaquine, robenecid (Col-Benemid®), rasburicase (Elitek®), sodium nitrite, sulfacetamide, sulfamethoxazole/trimethoprim (Bactrim®, Septra®), sulfanilamide, sulfasalazine (Azulfidine®), tafenoquine (Krintafel®),

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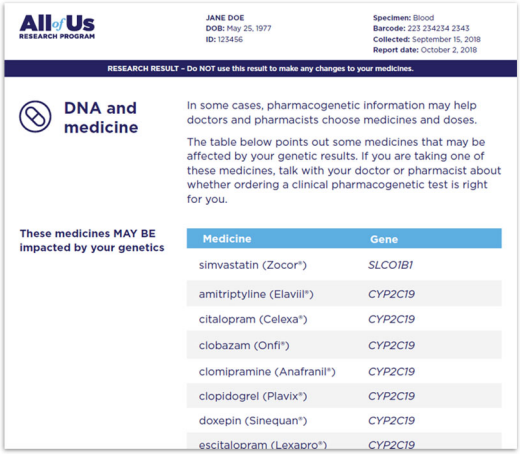
How is this implemented



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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*

Designed to encourage participant conversations with their providers by linking results to drugs:

"If you are taking one of these medicines, talk to your doctor of pharmacist to determine whether ordering a clinical PGx test is right for you"

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"Medicine and Your DNA" Report User Comprehension

205

Genetic-testing naive, non-*All of Us* participants

- 59.5% ≥45 years old
- 63.5% female
- 48.0% non-white
- 52.5% had an associate degree or less education

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")

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Education/support

How could finding out my DNA results help me?

Knowing your DNA results may help your healthcare provider take better care of you or you may learn something about yourself that you find interesting. Please watch this short video to proceed.

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Status and Updates

- IDE approval milestone achieved in July 2020

- Planned content updates
  - Expanded validations as controls are identified
  - Planned PGx targets with structural variation (e.g. *CYP2D6*)
  - New guidelines (e.g., *CYP2C9*)

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