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Precision Medicine and Pharmacogenomics: Propelling Practice and Proof in Populations

Creating a Research Program for All of Us

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#JoinAllofUs
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 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.

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>
<thead>
<tr>
<th>Table 1. Gene mutations associated with bicuspid aortic valve in human studies</th>
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</thead>
<tbody>
<tr>
<td><strong>Gene</strong></td>
</tr>
<tr>
<td>NOTCH1</td>
</tr>
<tr>
<td>ACTA2</td>
</tr>
<tr>
<td>TGF-β2</td>
</tr>
<tr>
<td>FNB1</td>
</tr>
<tr>
<td>KCNJ2</td>
</tr>
<tr>
<td>GATA5</td>
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<tr>
<td>Nkx2-5</td>
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<tr>
<td>SMAD6</td>
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Andrassî & Della Corte, Current Opinion Cardiology, 2016;31,6:586-592

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

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

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…”

“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
**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

- **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

- **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

*Based on diverse sampling and capacity
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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

HPO Network (Health Care Provider Organizations)
- UC San Diego Health
- UCI Health
- UChicago Medicine
- NorthShore
- Rush University Medical Center
- University of Illinois Chicago
- Northwestern Medicine
- Advocate
- Centene
- U.S. Pharmacological

RMCs
- All of Us California
- All of Us New England
- Trans America Consortium
- New York City Consortium
- All of Us Southern Network
- All of Us SouthEast Enrollment Center

All of Us Technology Systems Center (PTSC)
- UC San Diego Health
- UC Davis Health
- Cedars-Sinai
- UCI Health
- Northwestern Medicine
- Advocate
- Centene
- U.S. Pharmacological

Participant Technology Systems Center (PTSC)
- UC San Diego Health
- UC Davis Health
- Cedars-Sinai
- UCI Health
- Northwestern Medicine
- Advocate
- Centene
- U.S. Pharmacological

Biobank
- Mayo Clinic
- Smithsonian
- Partners
- UCI Health
- Northwestern Medicine
- Advocate
- Centene
- U.S. Pharmacological

Data & Research Center (DRC)
- VCU Health
- Columbia University Medical Center
- Northwell Health
- NewYork-Presbyterian
- Well Cornell Medicine
- Spectrum Health
- Reliant Medical Group
- University of Pittsburgh
- Temple University
- University of Arizona
- Banner Health

Genomics Partners
- Baylor Scott & White
- Johns Hopkins Medicine
- UTHSC
- color
- Partners Healthcare
- HudsonAlpha
- Virginia Commonwealth University

Communications & Engagement
- scripps
- BlueCross BlueShield
- DXC Technology
- EY
- Fidji
- Sage
- San Diego Blood Bank
- Walgreens
- WebMD

Partners
- University of Utah
- UMB

VA Medical Centers
- VA
- U.S. Department of Veterans Affairs

FQHCs (Federally Qualified Health Centers)
- VA Medical Centers
- Partners
- Genomics
- Data & Research Center (DRC)
- Biobank
- Participant Technology Systems Center (PTSC)
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
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
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
>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
Research Hub
ReSEARCHER WORKSHOP
Jan. 28 from 8am - 3pm


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
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
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.*

![Graph showing enrollment numbers from April 2017 to October 2019.](image)
Selected Data Snapshots

(Updated 10/21/19)

Gender Identity

Race & Ethnicity
Selected Data Snapshots

(Updated 1/12/20)

Age

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-29</td>
<td>12.8%</td>
</tr>
<tr>
<td>30-39</td>
<td>15.1%</td>
</tr>
<tr>
<td>40-49</td>
<td>14.9%</td>
</tr>
<tr>
<td>50-59</td>
<td>20.8%</td>
</tr>
<tr>
<td>60-69</td>
<td>20.7%</td>
</tr>
<tr>
<td>70-79</td>
<td>-12.2%</td>
</tr>
<tr>
<td>80-89</td>
<td>-3.1%</td>
</tr>
<tr>
<td>89+</td>
<td>-0.3%</td>
</tr>
</tbody>
</table>

Geography

All 50 states
Bilingual enrollment
Interactive mobile exhibits
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.
Coming Soon to the Research Hub: The Researcher Workbench

PUBLIC
- Data Browser
- Data Snapshots
- Survey Explorer

RESTRICTED
- Data Dictionary
- Concept Set Selector
- Cohort Builder
- Notebooks
- Help Desk
Data Release Timeline

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

**2019**
- 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.

**2020**
- 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

**2021 & beyond**
- 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.
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.

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.

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.
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*...
For more information...

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

@AllofUsResearch #JoinAllofUs

AllofUs.nih.gov

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Questions?