December 10, 2018

All of Us
Genetic Counseling Resource

NIH
OT-PM-19-001
Informational Webinar
What is the NIH All of Us Research Program?

The All of Us Research Program is a historic, longitudinal effort to **gather data from one million or more people** living in the United States to **accelerate research and improve health**. By taking into account individual differences in **lifestyle, socioeconomics, environment, and biology**, researchers will uncover paths toward delivering **precision medicine** – or **individualized prevention, treatment, and care** – for all of us.

“All of Us is among the most ambitious research efforts that our nation has undertaken!”

*NIH Director Francis Collins, M.D., Ph.D.*
What is the promise 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 genomic information.
- 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 is establishing nationwide engagement and recruiting infrastructure.
Major building blocks of the *All of Us* Research Program consortium

**DATA AND RESEARCH CENTER**
Big data capture, cleaning, curation, & sharing in secure environment

*Vanderbilt, Verily, Broad Institute*

**BIOBANK**
Repository for processing, storing, and sharing biosamples (35+M vials)

*Mayo Clinic*

**PARTICIPANT TECHNOLOGY SYSTEMS CENTER**
Web and phone-based platforms for participants

*Vibrent Health*

**THE PARTICIPANT CENTER / DIRECT VOLUNTEER**
Direct volunteer participant enrollment, digital engagement innovation, and consumer health technologies

*Scripps Research Institute (with multiple partners)*

**HEALTHCARE PROVIDER ORGS NETWORK**
HPOs with clinical & scientific expertise, enrollment & retention of participants

10 regional medical centers, 6 FQHCs, VA, totaling 165 enrollment sites

**COMMUNICATIONS & COMMUNITY NETWORK**
Communications, marketing, and design expertise; engagement coordination and community partners network

*Wondros, HCM, 34 community partner orgs, and future awards to grow network*
Selection of top Genome Centers in the U.S.
- Quality & quantity of data
- Return of results
- Intellectual capital

Currently on-boarding and establishing an effective consortium of Centers
- Genome analysis and RoR strategy
- Standardized outputs for research data
- Investigations of approaches to clinical interpretation and reporting
**All of Us Genomics: Overview of major deliverables and timelines**

- **Genome Centers:** genotyping and WGS capabilities + clinical analyses
  - May 2018: Funding Opportunity for *All of Us* Genome Centers (OT-PM-18-002 [link](https://allofus.nih.gov/sites/default/files/fa_genome_centers_OT_18.pdf))
  - 2019: Develop & test pipeline, including new AOU genotyping array (CLIA, FDA approval)
    - Launch data generation and analysis pipelines
    - Goal: 150k genotypes & 25k WGS

- **Launch Genetic Counseling program**
  - Nov 30: Genetic Counseling Resource Funding Opportunity released
  - April 2019: Award(s) for Genetic Counseling Resource (GCR)
  - Q2-Q3/2019: On-board GCR
  - Late 2019: Begin returning genomic results

- **Return of genomic results (ROGR) protocol**
  - ROGR pilot protocol for up to 40k participants
  - Jan. 2019: Deliver protocol to IRB
Challenges in Return of Genomic Results

1. All of Us is a research project – communication direct to participant, not provider
2. Need for genetic counseling
3. Need for medical referral
4. Negative results and risk of false reassurance
5. How to return PGx data, given that participant may not currently be treated with a relevant drug
6. 2nd party false positive results from return of raw data
Return of Genomic Results – What to return?

- **Medically Actionable Results**
  - ACMG59
  - Pharmacogenomics – CPIC A
  - Beyond 2019:
    - Carrier status
    - Poly-genic risk

- **Variant data file**

- **Non-medical information**
  - Ancestry
  - Traits
Genomic Data Returned

1. Medically-relevant
   a. PGx
   b. ACMG pathogenic (w/ counseling)
2. Access to ancestry
3. Raw data file available

Genome Analysis and Return of Genomic Results in All of Us
## Medically Actionable Variants (ACMG59)

<table>
<thead>
<tr>
<th>Type</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor Predisposition</strong></td>
<td>BRCA1/2, TP53, STK11, MLH1, MSH2, MSH6, PMS2, APC, MUTYH, BMP11A, SMAD4, VHL, MEN1 RET, PTEN, RB1, SDHD, SDHAF2, SDHC, SDHB, TSC1, TSC2, WT1 NF2</td>
</tr>
<tr>
<td>Breast/ovarian, Li-Fraumeni, Peutz-Jeghers, Lynch, Polyposis, Von Hippel-Lindau, MEN1/2, Medullary thyroid cancer, PTEN hamartoma syndrome, Retinoblastoma, Paraganglioma/pheochromocytoma, Tuberous sclerosis complex, WT1-related Wilms’ tumor, NF2</td>
<td></td>
</tr>
<tr>
<td><strong>Connective Tissue Dysplasia</strong></td>
<td>COL3A1, FBN1, TGFBR1, TGFBR2, SMAD3, ACTA2, MYH11</td>
</tr>
<tr>
<td>Ehlers-Danlos vascular type, Marfan, Loeys-Dietz, Familial aortic aneurysms and dissections</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td>MYBPC3, MYH7, TNNT2, TNIn3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA, RYR2, PKP2, DSP, DSC2, TMEM43, DSG2, KCNQ1, KCNH2, SCN5A</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy, dilated cardiomyopathy, Arrhythmia</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td>LDLR, APOB, PCSK9, ATP7B, OTC</td>
</tr>
<tr>
<td>Hypercholesterolemia, Wilson disease, Ornithine transcarbamylase deficiency</td>
<td></td>
</tr>
<tr>
<td><strong>Pharmacogenetic</strong></td>
<td>RYR1, CACNA1S</td>
</tr>
<tr>
<td>Malignant Hyperthermia</td>
<td></td>
</tr>
</tbody>
</table>
Medically Actionable Workflow

1. Participant has affirmatively consented to the use of their DNA for research purposes

2. Primary analysis (by sequencing or genotyping)
   - Data to DRC for research use

3. Clinical validation confirms medically actionable panel (does not include pgx variants)
   - Data to DRC for research use

4. Participant has affirmatively consented to the return of medically actionable genomic results

5. If variant is confirmed, medical director generates clinical report

6. Active return of result to participant by GCR
### Genetic information should be used to change prescribing of affected drug

<table>
<thead>
<tr>
<th>CPIC LEVEL</th>
<th>CLINICAL CONTEXT</th>
<th>LEVEL OF EVIDENCE</th>
<th>STRENGTH OF RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Genetic information should be used to change prescribing of affected drug</td>
<td>Preponderance of evidence is high or moderate in favor of changing prescribing</td>
<td>At least one moderate or strong action (change in prescribing) recommended.</td>
</tr>
</tbody>
</table>
Prominent labeling on reports directing questions to GCR

No 2nd/independent confirmation sample

Participant has affirmatively consented to the use of their DNA for research purposes

Primary analysis (by sequencing or genotyping) for targeted PGx variants in CPIC A genes

Data to DRC for research use

Participant has affirmatively consented to the return of medically actionable genomic results

Clinical reports generated through a CLIA/CAP process

Return of both positive and negative results to participant through participant portal (with supplemental participant and provider education materials)

+ variant(s) in CPIC A genes

no variants in CPIC A genes
All of Us Genetic Counseling Resource – Requirements

- Provide genetic counseling for pathogenic/likely pathogenic variant results from ACMG list with hand-off of participant to specialist care.

- PGx and ACMG non-pathogenic results will not be delivered by a genetic counselor but participants offered opportunity to contact GCR.

- Provide access to tele-genetic counseling to all participants, regardless of whether they have a positive or uninformative results. Integrate electronic tools (chat bot) to reduce trained personnel needs.

- Provide a “hotline” for primary health care providers to All of Us GCR.

- Provide access to genetic counseling to any individual interested in enrolling in the All of Us Research Program.

- Collaborate with All of Us on educational materials to accompany genome reports.

GC services at scale; many participants from low SES, some without access to health care services
1. Anticipated volume of services

<table>
<thead>
<tr>
<th>Budget Year</th>
<th>GC cases (annually)</th>
<th>Call Center Requirements (monthly contacts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yr1</td>
<td>3,000</td>
<td>2,000</td>
</tr>
<tr>
<td>Yr2</td>
<td>4,000</td>
<td>3,000</td>
</tr>
<tr>
<td>Yr3</td>
<td>6,000</td>
<td>4,000</td>
</tr>
<tr>
<td>Yr4</td>
<td>6,000</td>
<td>&gt;4,000</td>
</tr>
<tr>
<td>Yr5</td>
<td>6,000</td>
<td>&gt;4,000</td>
</tr>
</tbody>
</table>

2. Assumptions (deviation permitted in application, with justification)

A. Volume of case work = 2% of analyses (ACMG hit rate). Re-contact rate high. Each case allotted 2 hrs of GC time (1 hr prep + 1 hr counseling). No follow-up.

B. Service Center contact volume difficult to estimate. As many as 75% of contacts resolved with chat bot approaches? Asking applicants to build to 50 live calls/day.
Genetic Counseling Resource OT Funding Opportunity

• **Why Other Transaction?**
  1. Uncertainty of volume of services
  2. Likely evolution of workflows
  3. Extensive interaction with other awardees requires considerable NIH involvement

GCR is a central element in *All of Us* strategy
Genetic Counseling Resource Funding Opportunity: Objectives

1. Tele- / e-counseling service center + case work for return of ACMG pathogenic variants

2. Specific objectives: The Genetic Counseling Resource will be responsible for:
   A. Developing the capacity to provide genetic counseling call center services for participants (ultimately numbering > 1 million) in the All of Us Research Program and their healthcare providers,
   B. Delivering to a participant the clinical report of a finding of a medically-actionable monogenic disease variant and providing initial genetic counseling and hand-off to medical care,
   C. Contributing to the development of genetic/genomic educational resources for the program,
   D. Contributing to protocol development, for IRB and/or for regulatory agency review,
   E. Developing innovative technologies and approaches for population-scale genetic counseling services,
   F. Establishing strong collaborative relationships with other awardees contributing to the All of Us genomics platform, and
   G. Contributing to strategic planning for the program as a member of the All of Us Consortium.

Questions?
Other Transactions Authority

- The Other Transactions (OT) award mechanism is not a grant, cooperative agreement or contract.
- Only a few NIH Institutes/Centers have this authority.
- For the All of Us Research Program, the National Center for Advancing Translational Sciences (NCATS) manages the OT awards.
- All applicants (PI, AOR, Project Team) should read and be familiar with the Other Transaction Award Policy Guide for NIH Precision Medicine Initiative Research Programs. (The NIH Grants Policy Statement does not apply to OT awards.)
- OT allows NIH the flexibility to alter the course of projects in real-time to meet the overarching programmatic goal. This means awarded activity can be expanded, modified, partnered, not supported, or later discontinued based on program needs.
- If selected for award, applicants should expect significant ongoing involvement from NIH.
Submission Process

- All applicants must submit their application via the NIH eRA ASSIST System.
- To complete the application process, you must complete the NIH Commons Registration first. If you already have a Commons Registration, you do not need to re-register.
- The deadline for application submission is February 1, 2019 by 5pm local time.

Please start the registration and application submission process early to avoid a late application submission due to technical issues.

Late applications will NOT be accepted!
This presentation and Questions & Answers will be posted at https://allofus.nih.gov/news-events-and-media/events

http://JoinAllofUs.org

@AllofUsResearch
#JoinAllofUs

Precision Medicine Initiative, PMI, All of Us, the All of Us logo, and “The Future of Health Begins with You” are service marks of the U.S. Department of Health and Human Services.