December 10, 2018

All of Us Genetic Counseling Resource

National Institutes of Health

OT-PM-19-001

Informational Webinar

What is the NIH *All of Us* Research Program?

All of Us RESEARCH PROGRAM | The Future of Health Begins With You

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, totaling165 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

All of Us Genome Centers awarded Sept 30, 2018

- **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**

HGSC
HUMAN GENOME SEQUENCING CENTER

CIDR Center for Inherited Disease Research
Johns Hopkins University

BROAD INSTITUTE

PARTNERS HEALTHCARE

color

Genome Sciences
UNIVERSITY OF WASHINGTON

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 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

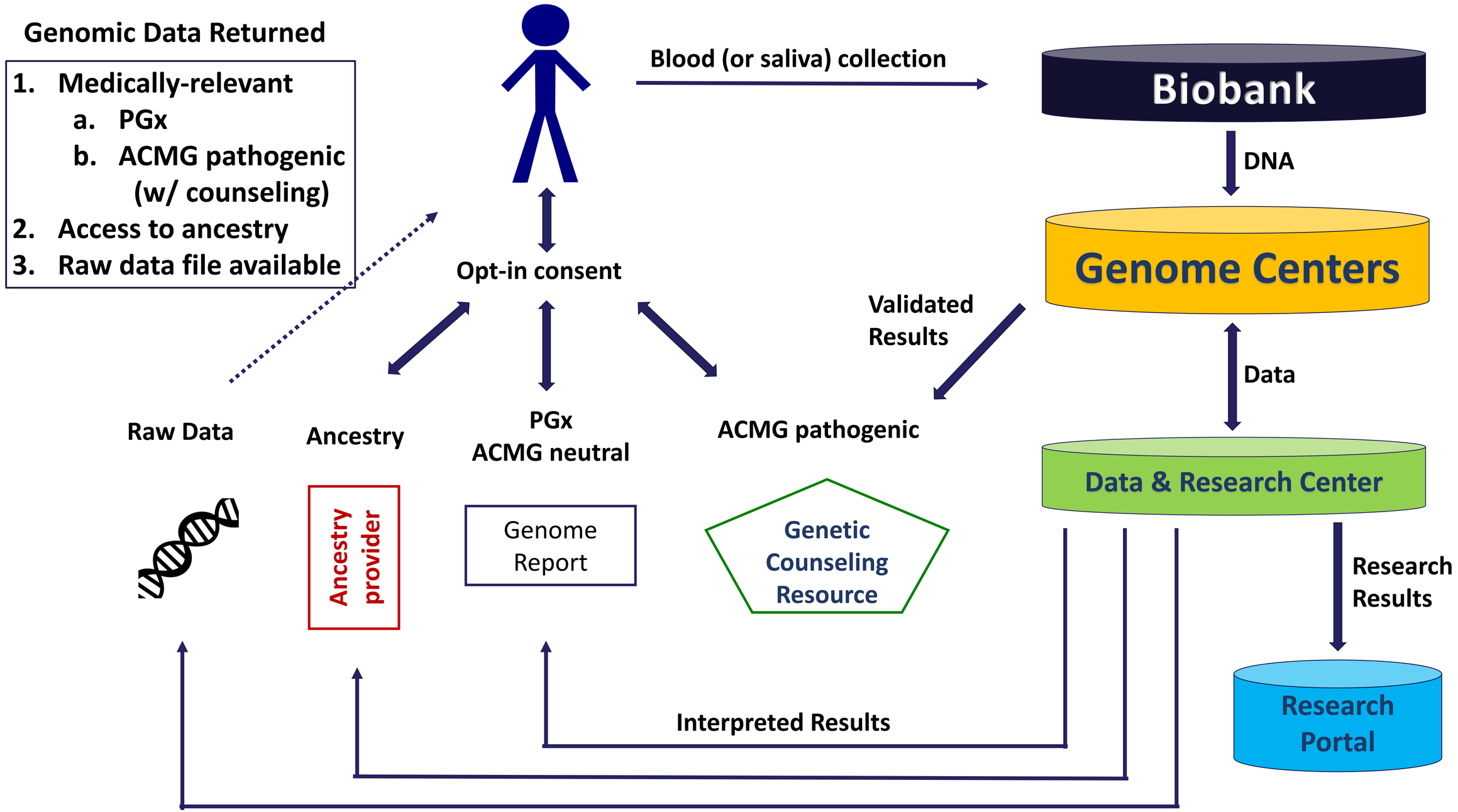
- Return of genomic results (ROGR) protocol
  - ROGR pilot protocol for up to 40k participants
  - Jan. 2019: Deliver protocol to IRB

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

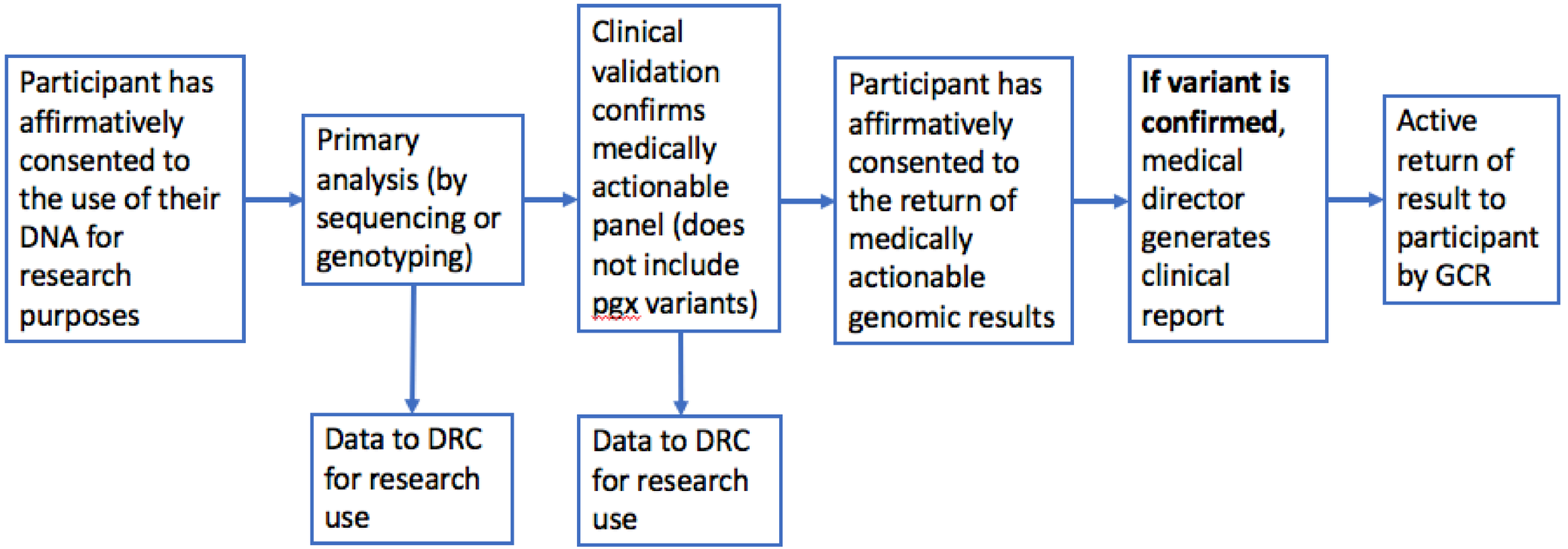


Genome Analysis and Return of Genomic Results in *All of Us*

Medically Actionable Variants (ACMG59)

Type	Genes
Tumor Predisposition Breast/ovarian, Li-Fraumeni, Peutz-Jeghers, Lynch, Polyposis, Von Hippel-Lindau, MENl/2, Medullary thyroid cancer, PTEN hamartoma syndrome, Retinoblastoma, Paraganglioma/pheochromocytoma, Tuberous sclerosis complex, WT1-related Wilms' tumor, NF2	BRCA1/2, TP53, STK11, MLH1, MSH2, MSH6, PMS2, APC, MUTYH, BMP1lA, SMAD4, VHL, MEN1 RET, PTEN, RB1, SDHD, SDHAF2, SDHC, SDHB, TSC1, TSC2, WT1 NF2
Connective Tissue Dysplasia Ehlers-Danlos vascular type, Marfan, Loeys-Dietz, Familial aortic aneurysms and dissections	COL3A1, FBN1, TGFBR1, TGFBR2, SMAD3, ACTA2, MYH11
Cardiac Hypertrophic cardiomyopathy, dilated cardiomyopathy, Arrhythmia	MYBPC3, MYH7, TNNT2, TNNi3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA, RYR2, PKP2, DSP, DSC2, TMEM43, DSG2, KCNQ1, KCNH2, SCN5A
Metabolic Hypercholesterolemia, Wilson disease, Ornithine transcarbamylase deficiency	LDLR, APOB, PCSK9, ATP7B, OTC
Pharmacogenetic Malignant Hyperthermia	RYR1, CACNA1S

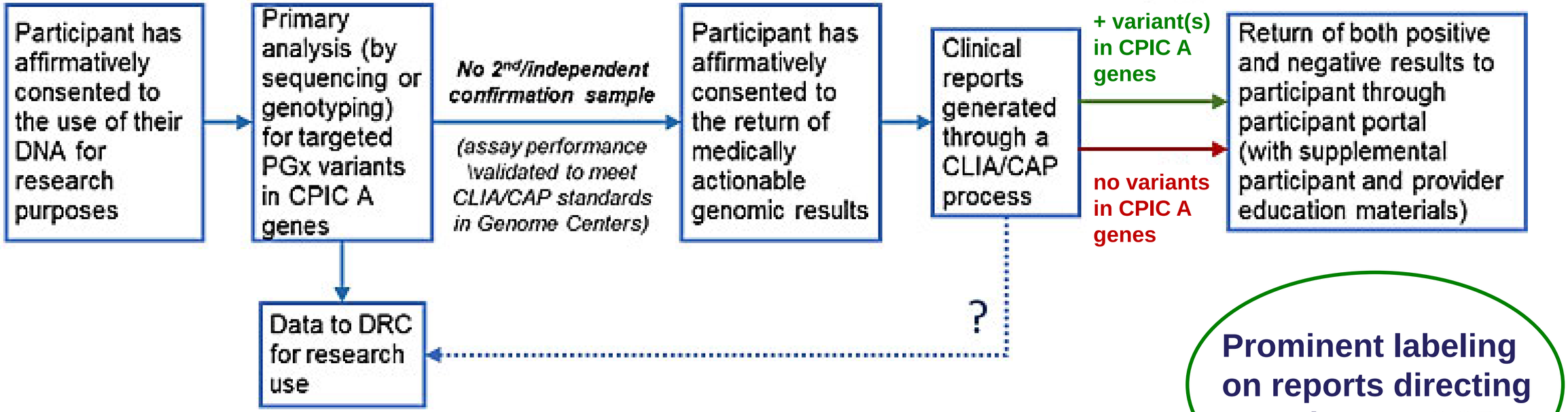
Medically Actionable Workflow



PGx: CPIC-A Guidance

CPIC LEVEL	CLINICAL CONTEXT	LEVEL OF EVIDENCE	STRENGTH OF RECOMMENDATION
A	Genetic information should be used to change prescribing of affected drug	Preponderance of evidence is high or moderate in favor of changing prescribing	At least one moderate or strong action (change in prescribing) recommended.

Pilot Project PGx Workflow



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

Genetic Counseling Resource Funding Opportunity Announcement

1. Anticipated volume of services

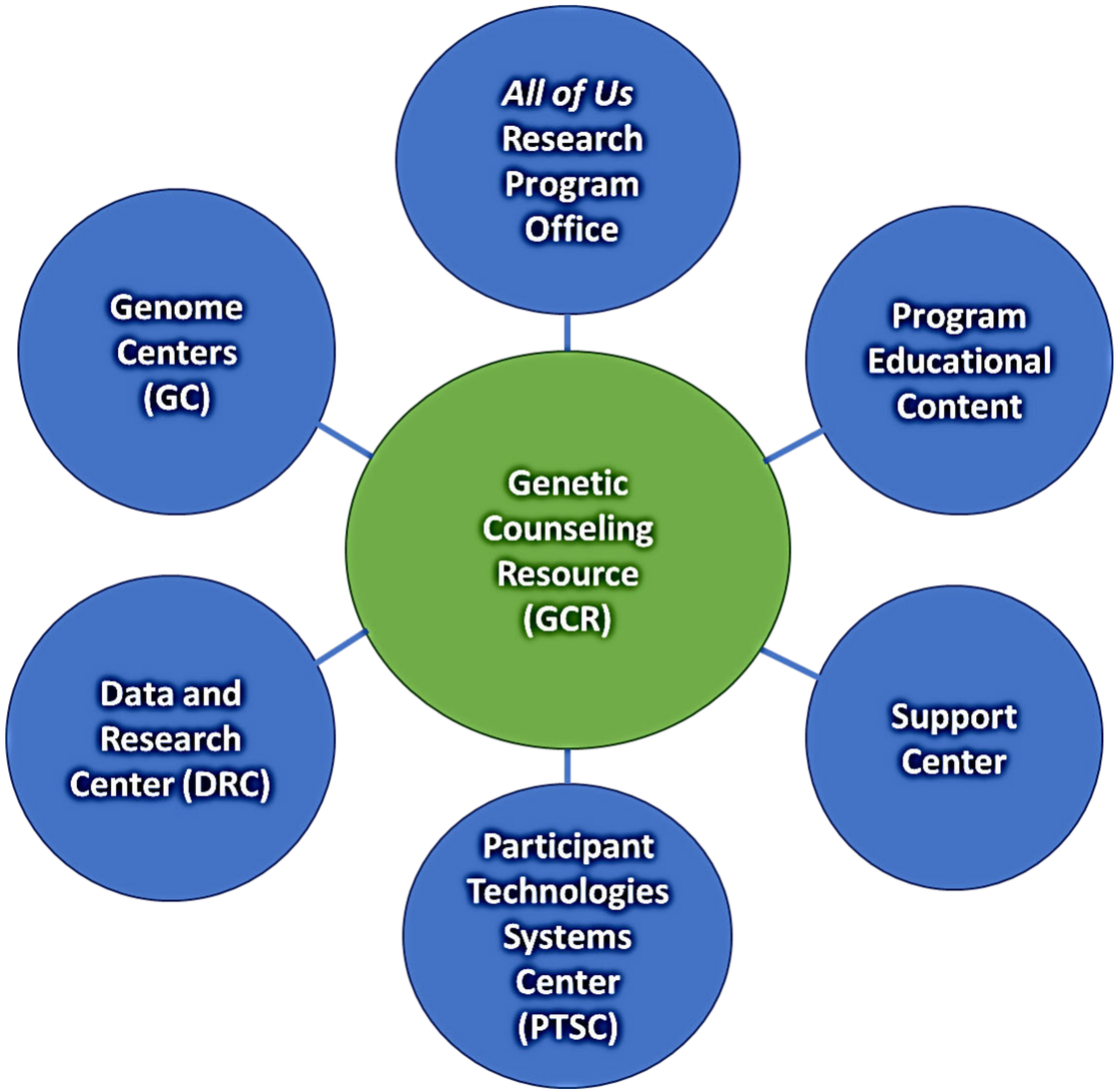
Budget Year	GC cases (annually)	Call Center Requirements (monthly contacts)
Yr1	3,000	2,000
Yr2	4,000	3,000
Yr3	6,000	4,000
Yr4	6,000	>4,000
Yr5	6,000	>4,000

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.

Scale

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

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