Overview Information

Funding Announcement Title	**_All of Us_ Research Program Genome Centers (OT2)**
Funding Announcement Number	OT-PM-18-002
Participating Organization	National Institutes of Health (NIH)
Components of Participating Organizations	This funding announcement is part of the NIH *All of Us* Research Program. The funding announcement will be administered by the National Center for Advancing Translational Sciences (NCATS) on behalf of the *All of Us* Research Program.
Announcement Type	New
Related Notices	NOT-PM-18-002 – Soon to be Issued Funding Announcement for *All of Us* Genome Centers (OT2) NOT-PM-18-003 – Notice Announcing Funding Opportunity Issued for the *All of Us* Genome Centers (OT2) and Applicant Webinar
Funding Announcement Purpose	The purpose of this funding announcement (FA) is to solicit applications for Genome Centers to generate and process genomic data as part of the *All of Us* Research Program. The *All of Us* Research Program seeks to create one of the world's largest and most comprehensive precision medicine research platforms with a data resource containing multi-layered data on one million or more participants. The *All of Us* Genome Centers will generate both genotype and whole genome sequence data from biospecimens from this cohort. These Centers also will operate an analysis workflow resulting in high-confidence calling of all variant types (single nucleotide variants, small insertions/deletions, larger structural variants including copy number variations) and establish a robust pipeline to securely transfer data to the *All of Us* Data and Research Center. Genome Centers awarded under this FA will be responsible for 1) developing the capacity and rigor necessary to achieve unprecedented scale of genomic data generation, up to 200,000 assays per year, 2) generating high-quality genotype and genome sequence data, with state-of-the-science variant calling, as a crucial data element for the *All of Us* data resource, 3) providing limited variant pathogenicity interpretation as an initial step in workflows for return of information to participants in the program, 4) deploying a fully compliant clinical validation workflow including generation of a clinical report for certain pathogenic variants defined by the program, 5) innovating for the advancement of technologies and approaches for population-scale genome analysis, 6) establishing strong collaborative relationships with other awardees supporting the *All of Us* genomics platform, and 7) contributing to strategic planning for the program as members of the *All of Us* consortium.

Funding Instrument	The funding instrument is the Other Transaction (OT) award mechanism: An OT award is not a grant, cooperative agreement or contract, and uses Other Transaction Authority.
Funds Available	The *All of Us* Research Program expects to adjust funds allocated for Genome Center awards on an annual basis, dependent on cost projections, programmatic requirements, and availability of funds. Applicants should not exceed $15M in direct costs for year 1 of the OT2 award application. Budget proposals for each of years 2-5 should follow the Cost Proposal guidance provided in the Required Application Content section.
Anticipated Number of Awards	NIH intends to fund one to two awards in FY2018.

Key Dates

Award Project Period	The total project period is anticipated to be five (5) years.
Post Date	May 23, 2018
Application Due Date	July 12, 2018 (5:00 pm local time)
Scientific/Technical Review Date	Review will be conducted on or around August 9-10, 2018.
Award Timeline	Award will be made upon selection and award negotiation. Earliest anticipated start date is September 2018.

Application Instructions

Required Application Content	Applications must include sufficient detail to allow the NIH and reviewers to assess the applicant's capabilities to successfully complete the award activities. All applicants must address and integrate all task areas. Eligible organizations may submit only one application. Applications must include the following with the total application package not exceeding 30 pages: • Technical Approach; not to exceed 15 pages. o Genotyping: Describe approach to acquire high-density genotype data for 100,000 or more specimens during yr1 of the award and for 200,000 or more specimens annually during yrs2-5 of the award. o Genome Sequencing: Describe approach to acquire whole genome sequence (WGS) data for 10,000 or more specimens during yr1 of the award. The program anticipates rapid increase in WGS assays during yrs2-5 of the award but the trajectory of that increase is dependent on numerous factors including cost of DNA sequencing, other programmatic goals, and availability of funds. Applicants should review Cost Proposal section for WGS target numbers. o Data Analysis: Describe approach and computational tools to be used to analyze genotype data. Describe approach and

	computational tools to be used to align and assemble genome sequencing data and to call variants. Applicants also should describe approaches to interpret variants in certain regions (defined in main body of this document) for pathogenicity or clinical utility. o Data Management: Describe methods and platforms for storing and managing data including generation of metadata/ancillary files to be transferred to the Data and Research Center (DRC). o Quality Assurance: Describe quality assurance measures to include specimen tracking, software change management, reagent or hardware change management, and other quality measures. o Regulatory Compliance: All data will be generated in a CLIA documented laboratory environment. Describe compliance measures and schedules including plans for compliance with applicable FDA regulations. o Innovation for population-scale genome analysis including cost reduction: Describe approaches to innovation in genome data generation and analysis to achieve greater scale. Include anticipated improvements in cost efficiencies throughout the award period. • Clinical Validation Laboratory; not to exceed 4 pages. *All of Us* intends to offer each participant enrolled in the program the opportunity to learn of the presence of dominant, actionable, pathogenic variants observed in the analysis of her/his genome. The program also may provide additional genetic information over time, still to be determined. Observation of such variants in genotype (and potentially genome sequence) data will require validation by clinical assay. Describe approaches to deploying clinical assays in a CLIA certified laboratory for such variants including generation of a clinical report. • PD/PI Experience and Key Personnel (Applicants should provide brief bios of key personnel); section not to exceed 4 pages. The level of effort these individuals anticipate committing to this project, if awarded, must be identified. Minimum levels of effort (LoE) are given in parenthesis below. Each application must identify the Program Director/Principal investigator (PD/PI LoE 25%) [or optionally, multiple PIs/PDs, LoE 20% each], a Project Manager (LoE 80%), and a Data Analysis Lead (LoE 50%). A list of other key investigators must be included. The individual with primary responsibility for quality assurance should be identified. An overall leadership structure and management plan must be included in this section. If there are multiple PDs/PIs, a leadership plan that incorporates a conflict resolution plan must be included. • Past Performance (Corporate/Organizational experience related to the funding announcement); not to exceed 2 pages. Applicants should describe or refer to the institutional record of performing the specialized work required in this project, particularly past experience in high-throughput genomic data generation.

- Cost Proposal; not to exceed 5 pages. Applicants must provide a milestone driven, cost allocated plan. Applications also must include budget proposals for genotyping and whole genome sequencing (WGS) assay annual throughput as described below. This will require three separate cost proposals for WGS elements in years 2-5 to account for differing WGS assay goals.

Budget Year	# Genotype Assays	# WGS Assays
Yr1	100,000	>10,000
Yr2	200,000	A. 25,000 B. 50,000 C. 100,000
Yr3	200,000	A. 50,000 B. 100,000 C. 200,000
Yr4	200,000	A. 50,000 B. 100,000 C. 200,000
Yr5	200,000	A. 50,000 B. 100,000 C. 200,000

  Guidance for annual budget maximums is not provided for yrs2-5. Applicants should propose budgets necessary to achieve the scale of data generation and analyses required for the stated throughput targets. Rationale for per unit cost reductions in out years should be provided. Cost models can include elements of cost-sharing, fixed price, or adjustable (cost reimbursable) or a hybrid agreement. The cost proposal must describe unit costs for genotype and whole genome sequence generation including the rate of indirect costs attached to these large-scale activities. Anticipated breakpoints in volume that drive lower price points should be noted
- Additional Requirements, to be included within above application segments. Describe 1) capabilities and experience in analysis of other 'omic data types such as RNA and microbiome., 2) concurrence with *All of Us* Research Program principles regarding the privacy and trust of participants, specifically, the Precision Medicine Initiative Data Security Policy Principles and Framework and Privacy and Trust Principles.

A one-page cover letter is not included in the 30 page limit. The cover letter must include the name and contact information for the authorizing organization representative and PD/PI(s). The letter must also include a statement and confirmation that the PD/PI(s) and authorizing organization representative have read and agreed to abide by the Other Transaction Award Policy Guide for the NIH Precision Medical Initiative Research Programs. Letters of support from

	partnering organizations/collaborators are also allowed and are not included in the page limit but are restricted to 12 in number. Other appendices are not allowed.
Instructions for Application Submission	This Funding Announcement includes a two-step submission process. All applicants are required to complete both processes. **All applicants must complete the Step 1 submission process on time in order for the application to be considered for review.** **Step 1:** Applications must be submitted in a single email attachment in PDF (Adobe) format to Ms. Irene Haas, *All of Us* Research Program Agreements Officer, at PMICPFOAInquiries@mail.nih.gov. Applications must be submitted by an authorized representative from your organization by 5pm local time. These applications MUST be submitted on time. Late applications will **NOT** be accepted. **Step 2:** NIH is piloting a new online submission process for Other Transaction (OT) applications via the NIH eRA ASSIST System. Applicants are required to complete this step, in addition to Step 1. Registration - To submit an application via ASSIST, the applicant organization must be registered in eRA Commons (see instructions). Organizations already registered in eRA Commons do not need to re-register. Once the organization is registered, the individual(s) with the role of Signing Official (SO) and Program Director/Principal Investigator (PD/PI) must be affiliated with the organization and have eRA Commons credentials to complete the submission process. Submission – The ASSIST system will not be available for application submission until June 9. After June 9, submit electronically via ASSIST (https://public.era.nih.gov/assist). Use **OTA-18-001** in field requesting Funding Opportunity Announcement. No penalty will be incurred if technical problems are encountered causing a late submission via ASSIST. Here are Instructions for submitting via the NIH eRA ASSIST system. In the future, instructions will also be available in the ASSIST online help (look for the OTA section). Technical help is available at the eRA Service Desk.
Eligibility Information	
Eligible Applicants	The following entities are eligible to apply as an applicant organization: Higher Education Institutions • Public/State Controlled Institutions of Higher Education

	• Private Institutions of Higher Education The following types of Higher Education Institutions are always encouraged to apply for NIH support as Public or Private Institutions of Higher Education: • Hispanic-serving Institutions • Historically Black Colleges and Universities (HBCUs) • Tribally Controlled Colleges and Universities (TCCUs) • Alaska Native and Native Hawaiian Serving Institutions • Asian American Native American Pacific Islander Serving Institutions (AANAPISIs) Nonprofits Other Than Institutions of Higher Education • Nonprofits with 501(c)(3) IRS Status (Other than Institutions of Higher Education) • Nonprofits without 501(c)(3) IRS Status (Other than Institutions of Higher Education) For-Profit Organizations • Small Businesses • For-Profit Organizations (Other than Small Businesses) Applicant organizations are encouraged to seek partnerships with all types of domestic organizations.
Foreign Institutions	Non-domestic (non-U.S.) Entities (Foreign Institutions) **are not** eligible to apply. Non-domestic (non-U.S.) components of U.S. Organizations **are not** eligible to apply. Foreign components are **not** allowed. Foreign components are defined as those responsible for performance of any significant element or segment of the project outside of the United States either by the award recipient or by an individual employed by a foreign organization whether or not OT2 award funds are expended.
## Application Review	
Objective Review Process	Applications will be evaluated for responsiveness to the FA requirements by NIH staff. Criteria include completeness of technical and cost elements, ability to achieve throughput goals with available funds, and institution/team experience in large-scale genomics. Responsive applications will be evaluated for scientific and technical merit by an appropriate review group convened by the NIH. Reviewers will evaluate applications based on the following: • Technical Approach • Plans and capabilities to achieve scale • Plans and capabilities to operate the Clinical Validation Laboratory • PD/PI and Key Personnel Experience

	• Past Performance • Cost Proposal Applicants may receive a brief written summary of the review. Successful applicants will undergo a negotiation process for award determination.
Evaluation Process	In addition to technical and scientific merit, applications will be evaluated for programmatic priority. Programmatic priority will be given to applicants with: • demonstrated genotyping and genome sequencing capacity to achieve throughput goals; • experience operating the most advanced genotyping and genome sequencing instruments; • demonstrated expertise in providing quality controls and assurances for generation and analysis of large-scale genomic data; • a record of effective data sharing including computational tools; • established CLIA certified operations; and • higher cost efficiencies in the application.
Questions Regarding this Funding Announcement and Program and Agreements Officer Contact	**Informational Webinar:** Thursday, May 31, 2018 from 12:30 pm-2:00pm EDT To register for this webinar and receive instructions, email: PMICPFOAInquiries@mail.nih.gov. Questions may be submitted via email, to Bradley Ozenberger, PhD, *All of Us* Research Program, for scientific/programmatic objectives, or to Ms. Irene Haas, *All of Us* Research Program Agreements Officer, National Center for Advancing Translational Sciences (NCATS), for award mechanism and application submission matters, both at PMICPFOAInquiries@mail.nih.gov.
Authority	Other Transaction awards will be made pursuant to current authorizing legislation.
All of Us Research Program Other Transaction (OT) Policy Guide	Other Transaction awards are subject to the requirements of the *Other Transaction Award Policy Guide for the NIH Precision Medicine Initiative*. Applicants must review this policy guide, which is available by accessing: http://www.nih.gov/sites/default/files/research-training/initiatives/pmi/20151118-ot-award-policy-guide.pdf

All of Us Research Program Genome Centers

Background

The *All of Us* Research Program is a participant-engaged, data-driven enterprise supporting research at the intersection of lifestyle, environment, and biology to produce new knowledge with the goal of developing more effective ways to promote health and treat disease. It is in part codified in the 21st

Century Cures Act which, among other things, mandates that the program consider the diversity within its cohort to ensure inclusion of a broad range of participants, including consideration of biological, social, and other determinants of health that contribute to health disparities. *All of Us* Genome Centers will be funded to generate both genotype and whole genome sequencing data from biospecimens from this cohort, with at least one million people in the core protocol which includes genome analysis. Genomic information produced from the Genome Centers will become a critical component in a comprehensive precision medicine research platform for investigators working on a variety of important health questions and is intended to be a national resource that will, over time, benefit the entire U.S. population.

The Genome Centers also will anchor a plan for responsible return of genetic information to participants in the program. *All of Us* is making extensive investments in returning value to participants in the form of the information that the program collects on each individual, including genomic information. This places additional responsibility on the Genome Centers to operate analysis pipelines to identify medically-relevant variants in certain genes as described in subsequent sections of this FA and to be compliant with federal and state regulations regarding genetic testing including the Clinical Laboratory Improvement Amendment (CLIA).

Considerations Toward a Comprehensive Genomics Strategy is a report from the *All of Us* Genomics Working Group convened by the program's Advisory Panel. Applicants may find this report useful as an additional source of background on *All of Us* intentions. It describes deliberations towards the following goals for a pilot phase: (1) test the generation, processing, analysis, interpretation, and sharing of genomic data in All of Us at a scale sufficient to enable planning for a genomic strategy for the full cohort; (2) pilot the return of clinically significant results to participants at a scale sufficient to inform the development and refinement of the return-of-results strategy and process; and (3) provide a genotype and phenotype resource that will add value above other existing genomic data sets and make this resource widely available to the research community in an efficient and non-burdensome manner. Since the publication of this report, the program has modified the scope as follows.

1. Genomic Data. Genotype data generation will not be piloted but rather the program expects to rapidly initiate genotyping activities shortly after Genome Center awards are made. Whole genome sequencing will be ramped up more slowly to build in the QA and analytic pipeline to the Data and Research Center (DRC) as well as to pilot approaches to managing these more complex data sets.
2. Return of Information. Return of genetic information to participants will be piloted, from both genotyping and sequencing platforms, largely as described in the report. Analyses associated with return of information to participants will be coordinated between Genome Center awardees and the DRC.
3. Research Resource. Data generated by the Genome Centers will be uploaded rapidly to the DRC for curation and inclusion in the *All of Us* research platform.

Purpose and Objectives of the *All of Us* Research Program Genome Centers

The NIH solicits proposals from US institutions (academic or private) or consortia of US organizations to serve as Genome Centers for the *All of Us* Research Program. Primary goals for the *All of Us* Genome Centers are to achieve unprecedented scale of genomic data generation (with approximately 200,000 or more genome-wide assays per year), to employ advanced variant calling pipelines to feed both the *All of Us* research platform as well as a return of information workflow, and to contribute to the advancement of technologies and approaches for population-scale genome analysis and its integration into precision medicine.

The specific research and data generation/analysis objectives for this FA are described below. All areas should be addressed in the Technical Approach section of the application.

Genotyping
All of Us Genome Centers will rapidly scale up high density genotyping while the pace of whole genome sequencing deployment is expected to be more measured. The application should describe an approach to generating high-density genotype data for up to 100,000 samples in yr1 of the award and 200,000 or more in each of yrs2-5.

The *All of Us* consortium has discussed with major manufacturers the possible content of a high-density array optimized for scientific return from the highly diverse *All of Us* cohort as well as return of value to participants in the form of potentially medically-useful variants, specifically, common pharmacogenomic markers and pathogenic variants in genes defined in the American College of Medical Genetics and Genomics (ACMG) Secondary Findings list. Awardees are expected to collaborate with the vendors and the *All of Us* Research Program consortium post-award to develop the specific array to be employed for *All of Us*.

Applicants should describe their rationale for development of an array platform for use in this project, as well as detail their process for genotyping and quality assurance, quality control. Data production costs should be reported as costs per sample, and should report estimated array costs separate from reagent, machine and labor costs. In describing this approach, applicants should start the process with quantified and quality-checked DNA samples, which will be provided to the awardee from the *All of Us* Biobank, and end the process with genotype data in a standard format and including assay metadata, which the applicant will upload to the DRC. Applicants should specify where proposed methods for genotyping are specific to a certain platform.

Genome Sequencing
The application should describe an approach to generating whole genome sequence (WGS) data for at least 10,000 samples in yr1 of the award and for three different targets in each of yrs2-5 as described in the Required Application Content section. Exome or other partial genome sequencing approaches are not acceptable.

Analysis methods to be implemented with this large-scale data production should be described in detail including: 1. alignment and assembly approaches taking into consideration the large proportion of non-European ancestry in the *All of Us* cohort, 2. variant calling, to include methods to identify structural variants effectively as well as other variant types such as repeat expansions, 3. haplotype elucidation, and 4. limited variant interpretation for medical utility, specifically, pathogenic and likely pathogenic variants in the genes on the ACMG list and common pharmacogenomic alleles (*e.g.,* CPIC level 1). Methods for pathogenicity determination of variants, including variants of unknown significance, should be described including the use of public resources such as ClinGen.

Applicants should describe standards and metadata/meta-analysis that they will incorporate to maximize the ultimate interoperability of the data produced in this project with other national and international sequencing projects. If multiple awards are made, all awardees will be required to harmonize analysis tools to ensure a consistent output across the program. Describe flexibility of proposed analysis pipelines to accommodate integration with other software tools.

Although cost per unit will be a major review consideration considering the scale required for *All of Us*, maximizing data quality is paramount to both enhance the potential for discovery and to ensure participants in the program will have the most accurate genome data the program can provide, within

the limits of the technology. The application should provide justification for the coverage model chosen and describe anticipated quality measures and cut-offs to be used in the variant calling methods.

The program may require additional time beyond this competitive grant period (5 years) to complete whole genome analysis on 1 million participants. Applicants should speak briefly to a vision for whole genome sequencing data and analysis in 2023 and beyond. How are assemblies likely to be improved? How might the Genome Center balance short read and long read technologies to enhance the identification of variants but maintain low cost? What analysis tools and public data resources may be useful to advance *All of Us* objectives?

Applicants should report sequencing costs, current and projected. Data production costs should be reported as cost per completed whole genome (at a quality at least as good as current high-quality high-throughput genomes). Average genome coverage should be described. Projections should extend to very large scale, up to 100,000 WGS assays in a year, and anticipated breakpoints in volume that would drive lower price points should be noted. Data production costs should include:

- Labor, administration, management, utilities, reagents, and consumables
- Sequencing instruments and other large equipment (include portion included in budget and amortization schedule)
- Any costs of CLIA certification requirements
- Informatics activities directly related to sequence production (e.g., laboratory information management systems and initial data processing)
- The Indirect Costs (http://oamp.od.nih.gov/dfas/faq/indirect-costs#difference) as they relate to the above items

In addition to genome sequencing costs, applicants are asked to report estimated costs of analysis through variant calling and pathogenicity interpretation on a per genome basis, for costs not included in data production. Comment on prospects for fully automating analyses for most or all variant types, including interpretations for pathogenicity. The estimates should include associated data storage costs, labor, administration, management, and indirect costs.

Applicants should indicate how *future* production and analysis costs will be reduced. Applicants should reference the cost and quality reporting elements described above so that reviewers can understand how costs will be reduced and have an overall understanding of how the budget requested relates to the proposed work.

Data Management

This section should discuss technical details that will enable data upload to the Data and Research Center (which uses a secure enclave on the Google Cloud Platform) at scale. It should include details about technical capabilities and IT infrastructure in place for the mechanics of data deposition, including its integration with the production and QC pipelines.

Variant calling format (vcf) files will be uploaded to the DRC from both genotyping and sequencing platforms. In addition, core sequence alignment data, CRAM file or equivalent, will be provided for the WGS data. Applicants should propose the metadata elements and structure to be included with these uploads, including descriptions of specific standards that will be used and approaches for updating files and file formats over the course of the project.

Note that no personal identifiers will be transmitted to the awardee. All samples will have unique numerical codes.

Quality Assurance
Describe methods and approaches to quality assurance for all stages of the operation, to include specimen tracking, software change management, reagent or hardware change management, and other quality measures. Separate QA methods should be described for genotyping and sequencing pipelines as appropriate. Demarcate those quality metrics which will be incorporated into metadata reports.

Clinical Validation Laboratory (CVL)
Observation of a pathogenic or likely pathogenic variant in the list of genes defined by the ACMG for reportable secondary findings will trigger validation of that variant using a certified clinical assay and the generation of a clinical report. Applications should describe the analysis workstream and subsequent reporting leading to the designation of a variant for clinical validation.

Applications to this FA must include a description of facilities and procedures for a clinical validation laboratory (CVL). The application should describe the leadership of the CVL including identity of the Medical Director, the date of most recent CLIA certification, and the genetic assays currently available.

The *All of Us* Research Program does not return results to the healthcare provider of participants but rather communicates findings directly to participants. The CVL within a Genome Center award will receive a test request and a DNA sample with a unique identifier, run a validation assay, and transmit a clinical report to an *All of Us* genetic counseling resource for communication of results to the participant.

A responsible return of genetic results strategy for the program will be initiated with variant data from the genotyping platform until which time workflows for this purpose are optimized from genome sequence analysis. Applicants should presume the following throughput for purposes of budget and resource planning although annual throughput may change during the grant period. Numbers are 2% (positive hit rate in ACMG genes) + 1% (false positive rate) of total genotype assays anticipated per year.

Validation Assays
Yr1 – 3,000
Yr2 thru 5 – >6,000 each year

Applications should discuss opportunities to improve confidence in variant calling and clinical reporting for ACMG genes using a whole genome sequencing assay. Applications should describe consideration of clinical-grade whole genome sequencing assays and requirements necessary to eliminate a secondary validation step. This includes considerations of federal and state regulatory compliance.

Applications from institutions or consortia without current capabilities to operate the CVL must describe in detail a pathway to acquiring these capabilities by time of award.

Technical Innovation for Precision Medicine
Successful awardees will have an opportunity to be at the forefront of precision medicine research and the application of genomic data into individual decisions for the betterment of health and well-being. Applications should describe research approaches for economically producing genomics data of maximum value for investigators and technical innovation to improve translation of large-scale genome analysis approaches to individual-level healthcare decision-making.

Additional Elements

Regulatory Compliance
Because the program will be returning information to participants, applicants must describe how they will comply with all statutory and regulatory requirements regarding genetic testing. Applications must include a description of laboratory CLIA certification, schedules, and include the Medical Director as key personnel in the award. If the applicant laboratory is not currently CLIA certified at the time of application submission, a detailed description of institutional procedures to obtain certification by time of award must be provided.

As described in the Clinical Validation Laboratory section, validation assays for program-specified ACMG gene variants must be fully documented for clinical use and assessed by an appropriate sanctioning body.

Applicants must also be in compliance with all applicable FDA regulations, specifically for Investigational Devices, prior to initiation of data generation. *All of Us* Research Program staff and the *All of Us* IRB will collaborate with awardees post-award to ensure compliance with FDA regulations.

Experience with other sequencing assays (*e.g.*, RNAseq, microbiome) of potential interest to *All of Us*
This FA requests proposals limited to genotype and genome sequencing data generation and analysis from provided DNA specimens. However, the program aspires to expand to additional types of nucleotide sequencing such as RNAseq, free circulating DNA markers, microbiome, mtDNA, etc. Applications should briefly describe experience and methods in other types of sequencing assays and approaches to employing these methods at large scale.

PD/PI and organization experience in large-scale genomic data generation and analysis
The scale of genome analyses required for the *All of Us* program exceeds any attempted by the NIH previously and will require exceptional leadership and prior experience with large-scale genome data generation and analysis. In addition, the Program requires maximization of data quality and confidence to ensure responsible return of information to participants. Applications should describe the experience of PD/PIs and other key personnel in the execution of large-scale genomic data endeavors. Current activities in genome analysis at the applicant institution or consortium institutional members should be described. Specify current resource (*e.g.*, instrumentation, personnel, facilities, etc.) requirements to expand these activities to achieve scale (up to 100,000 WGS assays/yr) for the *All of Us* program and how these requirements will be satisfied.

Other Transaction and Genome Center awards

The Other Transaction award mechanism allows significant ongoing involvement from NIH staff and provides the NIH the flexibility to alter the course of the project in real time to better meet the program's overarching scientific goals and to explore with awardees additional innovative ways to improve the genomics platform. This may mean that awarded activity could be expanded, modified, and partnered – or in some cases, not supported or discontinued--based on program needs, emerging methods or approaches, and availability of funds. Performance during the award period will be reviewed on a frequent and ongoing basis and milestone adjustments will be made as necessary.

Key Events	Dates	Action needed by applicants
Funding Announcement Posted	May 18, 2018	

Key Events	Dates	Action needed by applicants
Applications Due	July 12, 2018 **Step 1 MUST be completed on time.**	**Refer to the Instructions for Application Submission section for details.** **Step 1** - Email completed application as a single pdf file to PMICPFOAInquiries@mail.nih.gov by 5pm local time. Late applications will not be accepted. **Step 2** - Submit electronically after June 9 via ASSIST (https://public.era.nih.gov/assist), using Funding Opportunity Announcement number **OTA-18-001**. Applicants are required to complete this process in addition to Step 1. No penalty will be incurred if technical problems are encountered causing a late submission via ASSIST.
Review of applications completed	August, 2018	
DUNS and SAM number registration**	August 15, 2018	Potential award recipients must provide confirmation of DUNS and SAM number registration to PMICPFOAInquiries@mail.nih.gov
Estimated Earliest Award Date	September, 2018	

**DUNS and SAM number registration can take several weeks. Please see the registration link for helpful instructions. Awards require a DUNS and SAM registration. The registration link is specific to grants, however, the process for DUNS and SAM registration for this OT award is the same. Candidates should begin the registration process several weeks prior to this deadline to ensure completion in time to provide this information to NIH.

***All of Us* Research Program Organization and Governance Structure**

The *All of Us* Research Program functions as a Consortium, with all awardees considered to be members of the Consortium with specific roles in its governance structure. For example, the *All of Us* Research Program Steering Committee currently consists of the contact Program Directors/Principal Investigators (PDs/PIs) from each of the awards. The *All of Us* Research Program Consortium includes participant representatives in all aspects of its governance structure. Under the present structure, committees, task forces, and boards are established by the *All of Us* Research Program Steering Committee to oversee the development and implementation of Consortium activities. The governance structure may change periodically to meet the evolving needs of the program.

The *All of Us* Research Program has a single Institutional Review Board (IRB) constituted to ensure prompt and thoughtful consideration of the evolving protocols in the *All of Us* Research Program and the central importance of participants as research partners. The single IRB includes representatives of the participant community. Each awardee and any sub-awardees and enrollment partners will be required to establish an IRB reliance agreement with the Program.

Budget

Funds requested for salary support for all personnel must comply with the NIH Salary Cap in effect at the time of award.

Applications will use a budget model separating genome sequencing costs from other operational cost categories such as personnel, non-sequencing supplies, and miscellaneous costs. WGS data generation should be budgeted on a per-unit basis inclusive of indirect costs. More information about WGS budget requirements can be found in the Genome Sequencing section.

No separate equipment budget is allowed although equipment amortization may be included in per-unit costs.

Application PI/PDs and key personnel should plan for several weekly calls and team meetings as needed over the course of the award. In addition, three members from the awardee should plan and budget for up to four trips annually to Bethesda, MD, for *All of Us* Research Program Steering Committee and other strategic meetings.

Additional Requirements for Award

Maintaining the privacy and trust of *All of Us* participants and the security of their data are essential elements of the program. Applicants must be in compliance with the following *All of Us* Research Program Principles:

- Precision Medicine Initiative Data Security Policy Principles and Framework
- Precision Medicine Initiative Privacy and Trust Principles

Inventions and Patents

To promote the broad sharing of information and inventions in the *All of Us* Research Program, awardee inventions will be governed by FAR clause 52.227-13, which provides title to the Government in any invention made under this award, subject to a revocable, nonexclusive, paid-up license in each patent application filed in any country on a subject invention and any resulting patent in which the Government obtains title. This is to assure that patents directed to inventions made under this award cannot be used to block access by the research public to this important resource and associated technology.

(1) The Awardee shall include the substance of this patent rights clause in all third-party agreements for experimental, developmental, or research work. This patent rights clause must be modified to identify the parties as follows: references to the Government are not changed, and the third parties (subcontractor, sub-awardees, and vendors) have all rights and obligations of the Awardee in the clause. The Awardee shall not, as part of the consideration for awarding the third-party agreement, obtain rights in the third party's subject inventions.

(2) In the event of a refusal by a prospective third party to accept the clause, the Awardee—

a. Shall promptly submit a written notice to the *All of Us* Research Program Agreements Officer setting forth the third party's reasons for such refusal and other pertinent information that may expedite disposition of the matter; and

b. Shall not proceed with such third-party agreement without the written authorization of the *All of Us* Research Program Agreements Officer.

(3) In third party agreements at any tier, the agency, the third party, and the Awardee agree that the mutual obligations of the parties created by the patent rights clause constitute a contract between the third party and the agency with respect to those matters covered by this clause.

(4) The Awardee shall promptly notify the All of Us Research Program Agreements Officer in writing upon the award of any third party at any tier containing a patent rights clause by identifying the third party, the applicable patent rights clause, the work to be performed under the third-party agreements, and the dates of award and estimated completion. Upon request of the All of Us Research Program Agreements Officer, the Awardee shall furnish a copy of such third-party agreement, and, no more frequently than annually, a listing of the third-party activities that have been awarded.

Ownership of Data, Software, and Other Products

NIH will own all rights in data, software, and other products (collectively "Works") made or developed under this award, subject to a paid-up, nonexclusive, irrevocable worldwide license to reproduce, prepare derivative works, distribute copies to the public, and perform publicly and display publicly, by or on behalf of the awardee. The parties further agree that these Works are "works made for hire" as defined by the Copyright Act.

Award recipients agree that no commercial IP (*e.g.*, data, software or other products), whether owned by the awardee or a third party except those specifically referenced in the application, will be utilized without express prior permission of NIH.

Data Policies

All data generated by the *All of Us* Research Program, including the Genome Centers, are intended for use through the *All of Us* DRC. Though information may reside in the Genome Center during primary analysis steps and prior to upload to the DRC, Genome Centers must restrict their use of the data only to activities stipulated and characterized in the program.

All activities between the prime awardee, any sub-awardees, or other third parties will be required to conform to the *All of Us* Research Program approved protocols.

Awardees will be required to execute an Interconnection Security Agreement with the DRC to ensure the secure transfer of data. In addition, awardees are subject to security breach reporting requirements involving *All of Us* data.

Material Transfer Agreement

All awardees and partnering organizations will be required to comply with the established material transfer agreement below.

Any and all Material delivered pursuant to the award is understood to be experimental in nature and may have hazardous properties. The recipients of funds under this award, and any sub-awardees, may not make any representations and extend no warranties of any kind, either expressed or implied, with regards to such Materials. Unless prohibited by law, neither the recipients of funds under this award, nor any of their respective officers, directors, employees or agents shall be liable to the *All of Us* Research Program Biobank, for any direct, indirect, or consequential loss or damages arising out of the transfer, use, storage, or disposal of any such Material.

Institutions who receive Data and/or Materials under these awards are required to use Data and/or Materials only as outlined in the *All of Us* Research Program protocols, in a manner that is consistent with applicable state and federal laws and regulations, including any informed consent requirements and the terms of the institution's NIH funding, if any. Failure to adhere with this criterion may result in enforcement activities, including termination of award.

Human Subjects Requirements
The institution and personnel involved in the conduct of the research are required to comply with 45 CFR Part 46 and establish a reliance agreement with the *All of Us* Research Program central IRB. The NIH will issue all awardees a Certificate of Confidentiality to protect against the compelled disclosure of *All of Us* genomic data records and to support and defend the authority of the Certificate against legal challenges, per this Notice. Research activities are anticipated to be categorized as non-human subjects research as no direct personal identifying information will be provided to the awardee.

Termination/Expiration Requirement
A fundamental objective of this Other Transactions award announcement is to ensure that all specimens and data remain available without interruption to the research public, even in the event that awardees withdraw or are terminated or otherwise can no longer manage the project. Upon termination or expiration of this OTA award, NIH may take exclusive ownership, custody, and control of the resources generated by the All of Us Research Program, including specimens and data, at its reasonable discretion. For purposes of this solicitation, "exclusive custody and control" means that upon termination or expiration of this award, the departing awardee and its partners may not retain or disclose a copy of any data, and may not use any specimen (or portions thereof), acquired or generated under the award.

If the NIH decides to terminate this award, the termination of the award will be considered a unilateral change and the recipient will not have the right to appeal. Although a decision is made to terminate an award, the recipient must continue to comply with the Record Retention and Access, and Final Reporting requirements, and may need to sign a non-disclosure agreement to complete the termination process.