Key Insights

Ethical, Legal and Social Implications (ELSI) Considerations for the *All of Us* Research Program and Opportunities for ELSI Research

All of Us Research Program

November 2020

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1. Introduction

The *All of Us* Research Program hosted its Ethical, Legal, and Social Implications (ELSI) Research Priorities Workshop in June 2019. Attendees had the opportunity to explore publicly available data from the program and learn about data types that will be available in the registered and controlled tiers of the Researcher Workbench. On Day 1, attendees were asked to describe ELSI research questions, detail data and infrastructure needed to answer these questions, and develop research use cases. On Day 2, attendees shifted their focus to surfacing ELSI considerations for design and implementation of the *All of Us* Research Program itself. Small group work focused on topical areas that emerged organically from the open discussions. Attendees presented the key points of these discussions to the whole group and provided written summaries to the program.

2. ELSI Considerations for Program Design and Implementation

Through large group and small group discussions, attendees identified several important considerations for ethically robust program design, implementation, evaluation, and policy development. Using thematic coding, *All of Us* staff grouped the substantive feedback from attendees during and after the workshop into 10 overarching areas detailed below.

2.1. Data Use

Several ELSI issues raised during the workshop addressed different aspects of how *All of Us* data is used, particularly the prevention of harm (intentional or unintentional) from data use and enabling beneficial uses that align with participant and community priorities. In addition to monitoring user behaviors and taking enforcement actions against bad actors, attendees identified the need to limit specific data uses to prevent harm (e.g., profiling by providers of insurance or financial services). Attendees recommended that the program actively assess participants' views about data uses (e.g., alignment with participants' expectations or values, specific concerns participants may have, such as commercial use) through annual surveys, participant voting, periodic requests to assign value to research studies, and other approaches.

The possibility of allowing participants direct control over secondary data use was also discussed. One of the breakout groups developed a framework for ethical use of the *All of Us* resources with the following central criterion: "To be ethical, valuable research must be conducted in a methodologically rigorous manner" (Emanuel, 2000). To this end, they recommended that the program establish a "Methods Core" to ensure data quality and

appropriate methods for research use to produce better science and minimize stigmatizing research. Potential functions of the Methods Core included:

1. Create high-quality measures with variable definitions and complete codebooks.
2. Where feasible, assess survey measures for cultural differences in responses to sensitive questions. For example, mental health questions used in *All of Us* surveys may be validated in different populations, and those details will be available as part of the data quality information.
3. Create complex "constructed" variables that represent latent concepts, such as social status or class, health status, or community characteristics. Require researchers using the cohort data to either use the constructed variables or justify not using the constructed variables.
4. Where feasible, provide linked neighborhood- or community-level data for each recruitment site.
5. Determine how to ethically and responsibly combine individual- and community-level data.
6. On an ongoing basis, provide assessments of the inherent selection biases that differentiate the database from a representative sample of the United States or of smaller population groups that must inform conclusions drawn from analyses.
7. Provide statistical guidance for researchers who are used to inferential statistics applied to a sample of known populations.
8. Mandate rigor and ethical protections in use of qualitative data. If interviews are conducted as part of the program or approved research projects, those interviews should be shared in approved de-identified formats. The Methods Core should assist researchers in adhering to this mandate.

The *All of Us* Research Program was encouraged to actively collect data on and evaluate the topics or fields of research, the types of researchers accessing the data, and other aspects of data use to help identify areas where the program may need to develop or amend data access, use, and review policies. These data may also inform the program's scientific priorities and help identify areas where the program can actively enable community or other partnerships to foster beneficial research (e.g., to reduce health disparities, address unmet community needs). Attendees also discussed issues related to the composition of the Resource Access Board (RAB), its review and adjudication processes, and *All of Us* Data User Code of Conduct (DUCC) violation penalties. They expressed the need to integrate participant viewpoints in the review processes. Attendees noted that, while having a clear policy on stigmatizing research is helpful, operationalizing it would require careful deliberation to ensure useful research on sensitive topics and that research that some vulnerable groups consider important is not prevented (Sabatello, 2019). Some attendees recommended the program establish a separate participant review board to address concerns about unintended or unanticipated consequences of research projects and capture participants' broader views on the social value of research using *All of Us* resources.

2.2. Data Access

Attendees emphasized the need to ensure equitable data access for nontraditional researchers (e.g., citizen scientists, communities, patient- or participant-driven organizations, educators, students) and greater transparency on requirements for accessing the registered and controlled tiers of the Researcher Workbench. They also explored the role that participants themselves could play in determining data triage (such as which tier data belongs in, and at what granularity) and access by different types of researchers. Discussion also focused on participants' rights to access data for their own use, for their families' use, or for health care.

2.3. Data Collection

Attendees noted that *All of Us* must carefully weigh the risks of collecting additional data and the potential impact on participants, including participant burden, survey fatigue, and privacy risks. The attendees emphasized the need to remain inclusive in types of data collection, noting, for example, that no questions about history of pregnancy, pregnancy loss, infertility, and reproductive health were included in current surveys. The program was asked to consider the impact of the digital divide and its effects on inclusion of participants and their data in *All of Us.* Attendees noted that the program could also potentially benefit from additional data, especially to identify and address ELSI issues as the program, regulatory and policy, and technology landscapes continue to evolve. A group of attendees further delved into issues of data collection as they pertain to social determinants of health and health disparities, noting the need to extend the range of data elements (e.g., collect community-level or health system–level data) collected by *All of Us* that will allow sophisticated assessments of health disparities outcomes (Duran & Pérez-Stable, 2019; Institute of Medicine, 2003).

2.4. Understanding Participant Perspectives

Attendees highlighted the need to actively collect data to assess participants' perspectives on different aspects of the program, including:

- Motivations to participate
- Views on the types of data the program plans to collect (e.g., mental health or sensitive behavioral data, such as drug use or alcohol consumption)
- Concerns about data use, such as informational risk (e.g., privacy breach), dignitary harms (e.g., data use outside the scope of consent), or perceptions of group harm
- Privacy rights and value or benefit of the program
- Participant willingness to share different data types
- Changes in preferences for data use over time or postmortem

The program was encouraged to assess how these views vary across different groups of participants (e.g., by age, historically underrepresented in biomedical research [UBR][1] groups, family medical history, parental status). Some attendees raised concerns that lack of broader participant involvement (beyond participant ambassadors) in scientific vision planning processes could disenfranchise participants. They noted that without sustained participant input on research priorities, the program risks lower enrollment and poor retention, particularly among UBR groups.

Attendees noted opportunities to learn from the experiences of the Patient-Centered Outcomes Research Institute to understand participants' research priorities and set expectations for researchers. They recommended that the program explore new forms of participant engagement for setting priorities, such as establishing a peer-to-peer network for participants to communicate and push forward research agendas that they value. Other important perspectives considered included participants' perceptions of group harm, of the purpose and benefits of the *All of Us* Research Program, of therapeutic misconception, and of their rights as partners in research.

2.5. Mitigating Participant Risk

In addition to the risks associated with data use, the attendees explored ELSI issues related to representation of risks to participants. They recommended that the program assess whether consent language adequately and accurately conveys risks and that the informed consent process be evaluated periodically to ensure that the program is informing participants about new or evolving risks, particularly with new technologies for data analysis (e.g., artificial intelligence algorithms). They also suggested that the program explore models of dynamic consent that align with legal or regulatory changes.

2.6. Legal and Regulatory Issues

The evolving legal landscape of privacy, data protection, and other aspects pertinent to *All of Us* was considered an important challenge. Attendees noted that current U.S. laws provide inadequate protections for participants when a breach of confidentiality occurs, and additional protections should be considered. In addition to clearly communicating the terms of the DUCC to all stakeholders, some attendees suggested the program consider third-party enforcement for the DUCC, where participants would be the third-party beneficiaries who could take legal action if the DUCC was violated. They noted that the DUCC should outline enforcement processes and

[1] The populations the program considers underrepresented in biomedical research lie across the following categories: race, ethnicity, sex, age, sexual orientation, gender identity, income, educational attainment, disability, geography, and access to care. A detailed description is available on the *All of Us* Research Hub.

enforcement provisions, including injunctive relief. Some attendees recommended that data users be given the right to challenge any enforcement actions taken by the program.

2.7. Return of Value and Group Benefits

The attendees recommended that *All of Us* create processes for evaluating the program's impact on returning value to participants, groups, communities, and the public at large. Attendees emphasized the need to recognize the differences in power dynamics between and among participants, researchers, and the program and better understand what "value" means to participants in a longitudinal research context. Additional ELSI considerations focused on how the program's scientific resources can be leveraged to return value to groups and communities, particularly toward research that addresses health disparities and health inequities or the unique needs of UBR groups. The attendees called upon the program to actively explore ways to encourage community researchers to use its scientific resources—for instance, through potential pilot programs (or future seed grants) that could enable partnerships between traditional and nontraditional researchers—noting that previous passive models adopted by most other large databases (e.g., the database of Genotypes and Phenotypes [dbGaP]) have largely not succeeded in enabling or empowering community-based, minority, and underrepresented researchers.

2.8. Return of Results

Many of the ELSI issues raised and discussed focused on the return of results, especially the return of genomic results. Attendees emphasized the importance of gathering and assessing participants' experience with return of genomic results, including their expectations about what information is returned and how; their comprehension of results; and the psychosocial, behavioral, and economic impacts of results on participants and their families. This would help the program inform and adapt the process of returning genomic results to reduce ethical concerns. Ethical considerations raised included the influence of how information is conveyed (e.g., using terms like "medically actionable" in consent) on participant autonomy, potential for undue inducement to participate in some cases (e.g., where there is a family history of genetic diseases), and particularly for individuals from medically underserved groups and those who are unable to access genetic testing services. Some attendees worried about *All of Us* being perceived as a proxy for medical genetic testing and about returning results to participants without health insurance or access to specialty services, potentially reducing benefits to participants who are already disadvantaged. Some attendees also noted the risks of returning results due to gaps in current laws to prevent use of genetic information for determining eligibility for life, long-term care, and disability insurance.

Attendees also raised ethical concerns about the potential for negative, inaccurate (e.g., when pathogenicity or penetrance of variants is not well described), or uninformative results to provide false reassurance to participants who might then adopt potentially harmful health behaviors (e.g., not getting screened for breast cancer), especially among participants with lower

education and limited access to health services. They also highlighted the need to develop tools for educating the health care providers who would receive genomic results, as well as for returning results to participants who may face comprehension challenges and making the results more accessible to participants with low digital literacy, given the program's digital-first approach.

2.9. Governance

In discussions about the governance of *All of Us,* attendees recommended seeking input from external ELSI experts and researchers to inform policy setting, program implementation, and governance. Some attendees recommended that the program establish an external multidisciplinary review committee to regularly evaluate all aspects of the program and include diverse perspectives (participant, researcher, group, and community). Attendees emphasized that groups and communities are fluid constructs and that the program should recognize tensions between individuals and groups and communities when considering benefits and harms. Attendees also highlighted the need for fair, transparent, and accountable priority setting. They recommended more transparency about the *All of Us* governance structure to all stakeholders. Attendees also suggested the program use adaptive governance models, with periodic evaluations to adjust scientific priority setting, data collection, data access, and to enable research on health disparities or health needs of UBR groups. Additionally, they emphasized development of a clear sustainability plan for *All of Us* scientific resources (e.g., when the program ends) and integrating financial sustainability considerations into program evaluation.

2.10. Children and Adolescents in *All of Us*

The attendees observed that there are a host of legal and serious ethical considerations to examine before the program can open enrollment to children and adolescents. Attendees urged the program to begin with enrollment of parent–child duos or trios and ensure pediatric enrollment be initially done exclusively through health care provider organizations rather than the direct volunteer mechanism. The program was strongly encouraged to use identity verification tools when enrolling children. Attendees asked the program to address ELSI issues concerning recruitment; consent and assent; data privacy; data collection (e.g., self-reported data from children, measurements of social determinants of health in a pediatric context); parental access to child data and electronic health records, particularly for sensitive data (such as alcohol and drug use, sexual behavior, or abuse); whether and when a child should be able to access the participant portal; secondary data uses; and changes in preferences as children become adults.

Ethical issues raised included coercion in enrollment of children; therapeutic misconception, especially in cases where children have undiagnosed conditions; and potential harms of uncovering misattributed parentage, particularly when trios are enrolled. ELSI considerations discussed also included several aspects of the return of genomic results to children and

adolescents. The program was asked to consider preferences for the return of results from both child and parent(s), involvement of children in the return of results process (when to return results to children and how), and whether results on adult-onset conditions should be returned.

3. Opportunities for ELSI Research

On Day 1 of the workshop, attendees participated in facilitated group discussions around three thematic areas identified by the program: (1) genomics; (2) social determinants of health; and (3) legal, regulatory, and policy issues. Attendees were asked to record ELSI research questions, detail data and infrastructure needed to answer these questions, and develop research use cases[2] in these thematic areas. Attendees submitted nearly 100 normative and empirical research questions with a range of methods and topics. Some empirical approaches would leverage data available in the Researcher Workbench, while others proposed additional quantitative and qualitative data collection. The questions were collated, grouped, and coded thematically using the same 10 themes described in Section 2, with several research questions cutting across multiple themes.

The examples below and Appendix A illustrate the range of suggested topics, methods, and types of inquiry for ELSI research related to *All of Us.* Attendees also developed ELSI research use cases with data from the program and current projected technical capacities. These use cases also identified needs for additional data and technical capacities from the program for such ELSI research (see Appendix B).

The research questions listed are not in order of importance or level of relevance to the program. The questions and use cases are described as the attendees posed them, without interpreting their scope or intent. Table 1 provides examples of research questions for several ELSI themes.

[2] A use case outlines and describes a research question and includes the following requirements: (1) the data types needed to answer the research question; (2) the methods to obtain the data types and to analyze the data; and (3) the specifications for using the methods.

Table 1. ELSI Considerations and Sample Research Questions

ELSI Consideration	*Sample Research Questions*
Data Use	**What biases and trends are there in *All of Us* data use?**
Data Access	**Who accesses the participant portal for their information, how frequently, and why? What data do they access?**
Data Collection	**What are differences between EHR data collected versus data obtained from other sources, such as self-reported survey data or health insurance claims data (when provided)?**
Participant Perspectives	**What collective harms, if any, are participants concerned about?**
Mitigating Participant Risk	**How do different modalities of consent and recruitment affect comprehension of risks and values?**
Legal and Regulatory Issues/Implications	**How are local IRBs resisting/objecting to or modifying/interpreting *All of Us* policy and protocols?**
Return of Value and Group Benefits	**How does precision medicine research affect health disparities/inequities?**
Return of Results	**How does *All of Us* Set realistic expectations of risks and benefits of return of results? How *does All of Us* set expectations about a rare outcome?**

4. *All of Us* ELSI Research Needs: Filling ELSI Knowledge Gaps

All of Us will continue to find ways to facilitate ELSI research on the program or with program data. Although *All of Us* does not currently fund investigator-initiated research, the program wishes to facilitate ELSI research by leveraging support from, and collaborating with, NIH Institutes, Centers, and Offices (ICOs) and other funders. *All of Us* will also seek opportunities with NIH ICOs to convene workshops on specific topics (e.g., pressing concerns, emerging ELSI issues, gaps in the field) and identify shared ELSI research needs.

In addition, the program will identify opportunities for ELSI research that can be conducted within the consortium in a timely and rigorous manner—particularly in high-priority areas like return of genomic results and collection of wearables data—as part of pilot or demonstration projects for these program elements. *All of Us* will strive to communicate findings from such internal research to increase transparency in an ongoing way. The program will leverage existing opportunities to assess participant experiences (e.g., through participant feedback surveys at enrollment) to improve the quality of the program and will explore other ways to integrate ELSI issues in assessments of participant experience.

All of Us will continue to evaluate and learn internally about the issues related to data use, including the RAB review processes, the impact of RAB preventive or enforcement actions, and trends in research uses and types of users. The RAB is developing a rubric for periodic evaluation of its review processes and outcomes and a cadence for such assessments, which will help the program identify potential approaches to foster responsible use of data.

Building on insights from the workshop, *All of Us* is also working to identify areas for ELSI research that are relevant to the program in the near, medium, and long term. The program recognizes the need for, and encourages, all types of ELSI research (normative, empirical, and scholarship) on the program and with its data. *All of Us* can learn from and will integrate the extensive ELSI literature already available into its policies and processes. However, the program anticipates the need for additional research in some areas to address knowledge gaps. The topics described below are not intended to be an exhaustive list of *All of Us* ELSI research needs, but rather illustrative of areas where the scale, diversity, and temporal nature of the program, and precision medicine research in general, pose new and complex ELSI challenges and research opportunities.

4.1. Near Term (1–3 years)

- Explore and address the ELSI challenges of the return of genomic results (health-related, ancestry, polygenic risk scores) through a research program to potentially healthy individuals, longitudinally and across the spectrum of demographic diversity (racial or ethnic, socioeconomic, access to health care and resources).
- Better understand the range of ELSI issues surrounding broad access to data by nontraditional researchers, such as citizen scientists, community researchers, and educators.

4.2. Medium Term (3–5 years)

- Research focused on data use and its impact (e.g., potential for stigmatizing research, group harm, value generated) once the registered and controlled tiers are available.
- Filling important gaps in the literature about the validity and utility of data from wearables for diverse population groups. Many ELSI issues related to wearables and smart health (e.g., for the elderly, the underserved, those with disabilities, children) need further study.
- Research on governance and stewardship, as use of *All of Us* biospecimens is established over the next few years; specifically, research on balancing scientific priorities and community needs and priorities with benefits to communities (whether products and services are accessible and benefits equitable) will be important. *All of Us* and precision medicine research generally would also benefit from research on inherent biases in the *All of Us* data and biospecimens and those biases' impacts on different groups and communities.

4.3. Long Term (5–7 years)

- Research on the program's long-term impact on society and on health disparities and equity. These questions should also address the impact of advances in machine

learning– and artificial intelligence–based tools on mitigating or creating disparities in health care and health outcomes.

Working with the ELSI Brain Trust,[3] *All of Us* will periodically evaluate the state of the field, current and emerging challenges for the program, and gaps in knowledge to identify and refine its ELSI research objectives. The program will also solicit feedback from program consortium partners, participants, and community partners to identify priority areas for internal research. *All of Us* will also actively engage with NIH ICOs to identify shared ELSI research interests.

Conclusion

The *All of Us* Research Program received extensive and in-depth feedback on ELSI considerations for program design, implementation, evaluation, and policy development from the workshop attendees. These insights are valuable in guiding the program's activities going forward, including its ongoing engagement with participants, communities, the public, and other ELSI stakeholders. The ELSI Research Priorities Workshop was also very productive for exploring the breadth of potential ELSI research on the program, enabled by the program's data, and research needed to inform the program and assess its impact on health outcomes and disparities in the future. The exercises of developing ELSI research questions and use cases also helped surface additional data types, policy guidance from the program, and technological capabilities within the Researcher Workbench needed to enable a broad range of ELSI research. The program will explore ways to facilitate these, as detailed in the accompanying document *Ethical, Legal, and Social Implications in the* All of Us *Research Program.* The program will also continue to seek additional feedback on ELSI considerations to inform the program's activities and policies and to facilitate ELSI research, both normative and empirical, that can help the program build a platform for socially responsible and widely beneficial research.

[3] The program has established the ELSI Brain Trust, an internal working group composed of ELSI subject matter experts from the *All of Us* consortium and various NIH ICOs. The ELSI Brain Trust will help identify and consult on ELSI issues for priority activities of the program, working closely with the Policy Office.

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Glossary

AI/AN	American Indian/Alaska Native
CAPS	Committee on Access, Privacy, and Security
dbGAP	database of Genotypes and Phenotypes
DUCC	Data User Code of Conduct
DV	direct volunteer
EHR	electronic health record
ELSI	Ethical, Legal, and Social Implications
gROR	genomic return of results
HHS	Department of Health and Human Services
HPOs	health care provider organizations
ICOs	Institutes, Centers, and Offices
IRB	institutional review board
NIH	National Institutes of Health
PCORI	Patient-Centered Outcomes Research Institute
PMI	Precision Medicine Initiative®
RAB	Resource Access Board
SGM	sexual and gender minority
SME	subject matter expert
UBR	underrepresented in biomedical research

Appendix A: ELSI Research Questions Identified by Workshop Attendees

Data Use	• What does the Resource Access Board (RAB) look for when reviewing potentially stigmatizing research uses? What are the outcomes of the reviews? What changes do researchers make in response to RAB reviews? • Who requests access to the *All of Us* data? For what uses or research questions? Are they for-profit or nonprofit users? • What are the barriers or challenges to the access to and use of *All of Us* data? What justice concerns are raised? • What biases and trends are there in *All of Us* data use, in terms of types of data use requests and users? • How do participants feel about citizen scientists and for-profit companies using their data? • What are the products of *All of Us* data uses (e.g., downstream publications, press coverage)? How often does research with *All of Us* data use become stigmatizing? • Can the geospatial and environmental data collected influence how health insurers identify at-risk populations and, thereby, establish higher premiums for a specific community? • What kinds of findings are citizen scientists making using the *All of Us* data? What are their data use outcomes? What metrics can we collect on this? • Are citizen scientists reporting their findings from *All of Us* data and how?
Data Access	• Does obfuscation of data for privacy protection affect scientifically sound, generalizable scientific studies and results? • What data do participants decline to share and why (e.g., participants who consent to participate but decline to share electronic health records [EHRs])? • How do medical conditions affect the amount or type of data people are willing to share? • Who accesses the participant portal for their information, how frequently, and why? What data do they access? • Who is a citizen scientist? What makes them a citizen scientist? • Are there justice concerns related to who can access *All of Us* data?

Data Collection	• What are differences between EHR data collected vs. data obtained from other sources such as self-reported survey data or health insurance claims data (when provided)? What are the implications for secondary research and for health care of participants? • Who are the decliners? What are their reasons for declining to participate? • Do participation rates in *All of Us* vary across different subgroups (e.g., racial or ethnic groups, other demographic groups)? Do these vary by stigmatized behaviors such as high-risk health behaviors or by disease outcomes? • How comparable are *All of Us* participants' health data to local health data? Are they accessing more health care compared to the locally matched community? • How biased is the *All of Us* dataset? • What data on chronic disease or ongoing changes are collected? • What data on social determinants of health are available from health records? • What are objective indicators of "good" or "adequate" medical care? How does it map into self-reported data when we compare it to participants' medical records? • Would participant response and retention improve if they were paid for completion of surveys?
Participant Perspectives	• What individual harms are the participants worried about? • What collective harms, if any, are participants concerned about? • What are participants' definitions of privacy? How do they vary by subgroups of participants? How do they vary from those of researchers, ethicists, and citizen scientists? • What are the motivations of those who sign up to participate in *All of Us*? How do motivations vary across different groups of *All of Us* participants (by age, gender, belonging to an underrepresented in biomedical research group)? Do their experiences align with those expectations? • What incentivizes participation? • What are the reasons for participants to withdraw from *All of Us*? • What are *All of Us* participants' perceptions of risk and value for participating? How do they compare to other study populations? Are their expectations of value met? • What are the important dimensions of wellness at the level of individual, family, and community (not just equivalent to lack of disease)? • Who decides to link their data to other data types (e.g., Fitbit)? Why? • With whom do participants share their results? What happens when they take results to their health care providers?

Mitigating Participant Risks	• Do participants understand the trajectory of involvement they agreed to? Do they understand that they are not "partners" with secondary researchers who may use their data or invite participation in that study? • Which data types in *All of Us* should not be collected? Which data types or combinations of data types pose excessive risks for participants? • Do participants recognize that they are giving up control over their data? What drives participants' willingness to give up control of data to participate? What trade-offs are they making? Does that affect retention? • How does participant comprehension of risks and benefits compare at time of recruitment (initial consent) and over time? • How do different modalities of consent and recruitment affect comprehension of risks and values?
Legal and Regulatory Issues	• What are the privacy impacts of *All of Us* data use? • What are the frequency, legal, privacy, and social impacts of data breaches, inappropriate uses, or other deleterious impacts of data use? • When are data from an American Indian/Alaska Native person subject to tribal review? Is it when the tribe is identified? What if the participant lives in an urban setting? • How do the Health Insurance Portability and Accountability Act, the Privacy Act, and the European Union General Data Protection Regulation affect researchers' willingness to use *All of Us* data? • What rights do participants think they have? What is their understanding of rights in the event of a data breach? What is their understanding of state and federal laws (on privacy, data protection, etc.)? • How are local IRBs resisting or objecting to or modifying or interpreting *All of Us* policy and protocols?
Return of Value and Group Benefits	• How do different participant groups define benefit? What are objective indicators of benefit? Who benefits from participation in *All of Us*? • How does precision medicine research affect health disparities or inequities? What types of value are being generated by different types of data users in the registered tier?

Return of Results	• What factors and values drive the choice to receive or decline return of genomic results (gROR)? • What are the most effective ways to maximize an “informed choice” about gROR? • Which genomic results do participants want, and why do they want them? • What are participants’ expectations of gROR, and how do they differ between groups? • How do we set realistic expectations of risks and benefits of return of results? How do we set expectations about a rare outcome? • Will implementation of return of results be fair and equitable, given that the program has chosen a digital approach for doing so? • What genomics education approaches are effective (i.e., online vs. face-to-face vs. community-based)? How do these vary by different groups (racial or ethnic groups, socioeconomic groups)? Does that change decisions to get back results and how participants respond to results? • How much genetics or genomics education can be integrated during the consent process? • What community engagement approaches are needed, and how do they compare to set realistic expectations about gROR? • Are participants concerned about genetic privacy? Do views vary across different groups, and how do they affect consent to gROR? • How do people react to or understand different types of results? How do they understand negative results (i.e., non–health-related changes reported) and probability (uncertainty)? • How do we reduce the risk of and educate against false reassurance? • What are the barriers to understanding, and how do they vary across different groups? How can we improve comprehension of results? • How do participants respond to different modalities of return (text, phone, in-person, chat bot)? Which approach is best suited for different groups of participants (e.g., socioeconomic, educational, spoken language)?

Return of Results *Continued*	• What metaphors do people use and think about for genetics? Does it vary by culture? • How do people understand the difference between biological inheritance and cultural transmission? • How do we help participants understand familial impact? • What are the psychosocial, behavioral, economic, and health impacts of gROR? • How do we customize approaches to gROR to reduce harm? Should there be pre-screening for conditions that could affect their response (e.g., depression, anxiety disorders)? • How do the experiences with gROR and the impacts vary between direct volunteer participants vs. participants recruited by health care providers? • How do the experiences with gROR and the impacts vary between direct volunteer participants versus participants recruited by health care providers? • How do participants respond to differences between self-identified racial or ethnic identity and actual genomic ancestry findings? • How does gROR affect participants' other decisions (e.g., interest in other results, *All of Us* participant portal use, retention, engagement with *All of Us*)? • Does the program have obligations for follow-up required for participants' family members upon gROR, and if so, what are they? • Who is accessing genetic counselling services, and are there disparities in use? • Is gROR an intervention? • How do we prepare health providers for receiving genomic results, especially in low-resource settings? • Can all participants take equal advantage of the results and medical actions that will result from gROR (e.g., uninsured, participants with limited access to health care, participants with physical and cognitive disabilities)? • What resources or needs do participants have to share their results with health care providers? • How do we measure benefit to individuals, groups, communities, and society from gRoR? How will risks to them be mitigated?

Appendix B: Examples of ELSI Research Use Cases Developed by Attendees

A use case outlines and describes a research question and includes the following requirements: (1) the data types needed to answer the research question; (2) the methods to obtain the data types and to analyze the data; and (3) the specifications for using the methods.

ELSI Theme: Participant Perspectives
Cross-Cutting Theme: Return of Results
Example Research Question: What are reasons that individuals (current *All of Us* participants or potential participants) decline to participate in:

- The *All of Us* Research Program overall?
- The *All of Us* genomics protocol?
- Return of results from *All of Us* genomics?

Data Type	Method	Frequency of Data Collection
Participant decline rates	Collected by the program during enrollment or consent process	Ongoing basis
Participant demographics	Data collected by the program	Ongoing basis
Participant responses	Surveys, interviews, feedback collected during consent process	Ongoing basis

ELSI Theme: Data Collection
Cross-Cutting Theme: Participant Perspectives
Example Research Question: How willing are participants to answer questions about mental health and substance use compared to other kinds of health conditions and health-related behaviors?

Data Type	**Method**	**Frequency of Data Collection**
Participant response or nonresponse rates	Survey on mental health, substance abuse, other health-related modules	Ongoing basis
Participant demographics	Data collected by the program	Ongoing basis

ELSI Theme: Return of Results
Cross-Cutting Theme: Return of Value and Group Benefits
Example Research Question: Can all participants take advantage of the results and medical recommendations that will result from *All of Us* return of results? Would this benefit the uninsured participants, those who do not regularly see health care providers, or those with disabilities (physical and cognitive)?

Data Type	Method	Frequency of Data Collection
Insurance coverage	Survey, EHR	Ongoing basis
Participant demographics	Data collected by the program	Ongoing basis
Educational level or socioeconomic data	Data collected by the program	Ongoing basis
Health care utilization	Survey, EHR	Ongoing basis
Health care spending	Survey	Not specified
Address, geographic location urban or rural (ZIP code), homelessness	Survey, EHR	Ongoing basis
Distance to medical facility, type of health facility	Health system data,*geocoded data*	Not specified
Disabilities	Survey, EHR	Ongoing
Diagnoses	Survey, EHR	Not specified
Prescription drugs	EHR	Ongoing basis

*Data currently not collected by *All of Us*

ELSI Theme: Return of Results
Cross-Cutting Theme: Participant Perspectives
Example Research Question: What can we do to improve comprehension? How well do participants understand negative results? How well do participants understand probabilities and uncertainty in genetic test results?

Data Type	Method	Frequency of Data Collection
Genomic literacy	Survey*#	Not specified
Previous experience with genetic testing	Survey*#	Not specified
Participant demographics	Data collected by the program	Ongoing basis
Participant experiences with return of results through *All of Us*	Participant interviews*#	Not specified

*Data currently not collected by *All of Us*
#Participant recontact needed

Appendix C Attendees of the ELSI Research Priorities Workshop

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