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SYSTEMATIC REVIEW

The research participant perspective related to the conduct of genomic cohort studies: A systematic review of the quantitative literature

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Abstract

Observational genome-wide association studies require large sample sizes. Evaluating the interplay between genomic, environmental, and lifestyle factors can require even larger sample sizes. The All of Us Research Program will recruit 1 million participants to facilitate research on genomic, environmental, and lifestyle factors. Integrating participant preferences into the research process is a new paradigm and a necessary component of the All of Us Research Program. The purpose of the study is to summarize quantitative studies of participant preferences related to participation in observational genomic research studies, starting with consent through return of results. Integrating this information into the conduct of genomic studies may benefit participants, and improve participant satisfaction, recruitment, and retention. We conducted a systematic review of the literature regarding participant views related to reconsent and broad consent, use of de-identified data, contribution of data to a biorepository, risk of identification, return of individual genetic results, and motivation for participation in genomic studies. Twenty-three articles met our inclusion and exclusion criteria. Study results found that most participants support broad consent; however, significant differences related to reconsent preferences have been shown by gender and age. Most participants support the return of individual genomic results and do not feel it is necessary to maintain a link to their de-identified data. Reasons given for joining research studies varied by population source. These findings, in addition to the knowledge that participants are more accepting of broad informed consent methods when the *rationale* is explained, can assist in developing guidelines for future observational genomic research.

Keywords

Informed consent, Reconsent, Broad consent, De-identification, Participation, Return of results

Implications

Practice: Understanding participant perspectives regarding reconsent and broad consent, use of de-identified data, contribution of data to a biorepository, return of individual genetic results, and motivation for participation will enable researchers to maximize recruitment and retention and minimize participant burden and participation bias for future genomic observational research studies.

Policy: Participant perspectives from public, research, and clinical populations, as well as all demographic groups, must be considered when developing informed consent practices for observational genomic research studies.

Research: Next steps research should build from this review to conduct quantitative and qualitative research on the long-term positive and negative effects of individuals and families incorporating genomic testing results into their future choices and behaviors.

Introduction

Made possible by rapid advancement in genomic sequencing technologies as well as advances in health information technology [1], the new *All of Us Research Program* is tasked with learning about disease risk, discovering new disease biomarkers, expanding our knowledge of pharmacogenomics, and finding targeted and individualized treatment of diseases [2, 3]. To facilitate this goal, the All of Us Research Program will enroll one million participants into a diverse research cohort of well-characterized participants. The scale and complexity of this project will necessitate consideration and review of policies and procedures related to human subject protections, and importantly also requires input of the participants themselves on such issues as participant reconsent, return of individual genetic research results, and sharing of data with biorepositories.

Human genomic research and advances in technology have prompted a recent overhaul of many federal regulations designed to protect human subjects [4]. The Federal Policy for the Protection of Human Subjects or "Common Rule" was written as a guide to protect the rights of human subjects. Principles in the original Common Rule, however, did not address current research issues such as biobanks, electronic

data, or health records. A recent update to the Common Rule will include several changes from current requirements [5, 6]. Some of these changes include informing participants about: (i) whether clinically relevant and/or individual genetic results will be returned; (ii) broad consent for use of identifiable biospecimens in future, unspecified research studies; (iii) broad consent must inform participants that research results may not be returned to them; and (iv) broad consent must inform participants that it is possible that identifiable data or biospecimens will be used for secondary research without additional consent. This Common Rule update has been approved with scheduled implementation in 2018. It is important to understand how these Common Rule changes to informed consent and the return of individual genetic results will be viewed by research participants, a key group of stakeholders. It is possible that negative attitudes may impact future participation and retention in observational genomic research.

Overall, volunteerism among research participants has decreased in the United States [7]. Increasing numbers of research studies have resulted in an increased feeling of intrusion among participants or impression that their participation is not as valuable. In addition, an increase in telemarketing and political polling may be difficult for participants to distinguish from scientific studies, and the increased complexity of research studies may make participation too burdensome for the participant [7]. At a time when participation in epidemiological research studies has been declining, the All of Us Research Program strives to create a cohort of historic size. To ensure the success of this program, it is necessary to include research participants' views and preferences regarding consent models (e.g. reconsent and broad consent), use of their data (e.g. de-identification, contribution to a biorepository), and return of individual genetic results, and how these views fit with recent informed consent changes. The importance of respecting participant preferences is emphasized by the Precision Medicine Initiative Privacy and Trust Principles [https://www.whitehouse.gov/sites/default/files/microsites/finalpmiprivacyandtrustprinciples.pdf]. Describing findings on participant preferences that are generalizable to broader groups and give an objective assessment that can be adapted for large cohort studies will provide a foundation to improve decision-making regarding human subject protection policy guidelines. Furthermore, the new research paradigm where participants are considered research partners could benefit participants in a number of ways, including reducing participant burden, and may improve participation and retention of more diverse groups.

This study will systematically review the quantitative literature related to views about reconsent and broad consent, use of de-identified data, contribution of data to a biorepository, return of individual genetic results, and motivation for participation in observational genomic studies from the adult research participant perspective. Summarizing the most recent literature on these topics may inform the conduct and facilitate integration of participant preferences into large-scale genomic studies.

MATERIALS AND METHODS

A systematic literature review was completed using the PRISMA statement as a guideline [8]. An electronic search of PubMed and Web of Science databases was done using four separate searches and including the MESH and title/abstract word (tiab) terms: (i) data sharing (tiab), genetic research (MESH), attitudes (MESH), perspectives (tiab), participant (tiab); (ii) reconsent (tiab), broad consent (tiab), public opinion (MESH), views (tiab); (iii) genetic research (MESH), health research (tiab), public opinion (MESH), reasons to participate (tiab); and (iv) return of genetic results (tiab). Searches contained all the literature published through March 7, 2017 to include current views related to participant perspectives. Titles and/or abstracts of these publications were reviewed by two independent reviewers for potential eligibility, and a third reviewer was used as an arbitrator. Inclusion criteria included peer-reviewed studies published within the past 10 years, quantitative studies (defined as studies which use structured data collection techniques and statistical data analysis), and studies which include adult participants (at least 18 years old). A 10-year time frame was used as the relevant period to review this literature because it was felt that recent advances in genomic sequencing health information technologies began during this time. Exclusion criteria included review papers, qualitative studies, and those not published in English. In addition, this review did not include studies which evaluated participant views related to the return of genetic results as a result of their medical care in a clinical setting (compared with the return of genetic results as a result of research participation). While two studies included a mixed-methods design, this review reports only on the quantitative results. Qualitative studies will be the subject of a separate review and were excluded here to conform to page limitations.

The flow of information through the phases of this systematic review is shown in Fig. 1. In total, 2,692 publications were excluded for the following reasons: published greater than 10 years ago (n = 2,673), sample size <39 (n = 2), or were duplicate records (n = 16). Publications were also excluded that were qualitative studies (n = 36) or irrelevant to this review (n = 6,776). Reasons varied, but most irrelevant studies fell into one of the following categories: research involved disclosure of genetic test results in a medical treatment setting,

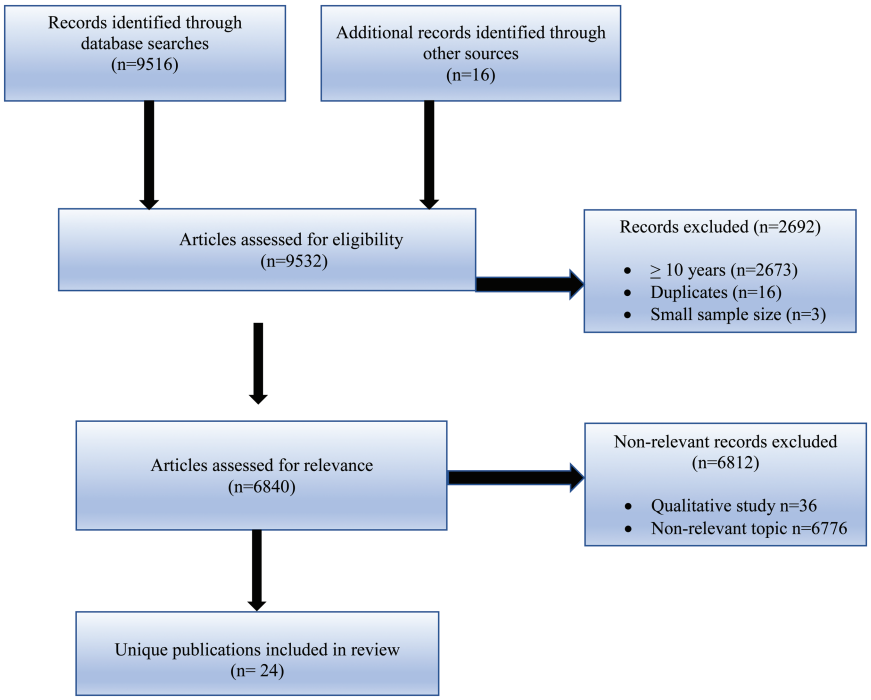

Fig. 1. | Flowchart of information through the phases of this systematic review

research population was limited to parental consent for use of minor data, or focus was not one of our defined topics.

The bibliographies of all included studies were checked carefully to identify additional studies which were not included in the original search and 16 additional records were identified. The full article was obtained for all publications that appeared to fit the inclusion and exclusion criterion.

Information was extracted from all included studies and included bibliographic information, the study population, including inclusion/exclusion study criteria, age, race/ethnicity, participant selection from the general population (participants not currently enrolled in a genomic research study) versus a research population (participants currently enrolled in an exciting genomic research study), sample size, study design, and outcomes relevant to review (Tables 1 and 2).

Two authors independently extracted this information and any discrepancies between the two extractors were resolved by a third researcher. All relevant findings that are reported in this review employ the terminology, percentages, and format used in the publications. Two publications used a mixed studies methodology; however, this review reported only the quantitative findings.

RESULTS

Publication descriptions and study characteristics

Tables 1 and 2 show the 23 publications that met our inclusion and exclusion criteria [9–31]. These studies varied in size, with the largest study population including 4,961 participants and the smallest study comprising 100 participants. Most studies used a cross-sectional survey design (n = 22), followed by an experimental (n = 3), and observational cohort design (n = 1). Participant ages ranged from 18 to 102 years, and most study populations had a majority of women and were predominately white.

Reconsent and broad consent

Eight studies provided quantitative results related to views about reconsent and broad consent for genetic studies from the participant perspective [9–16]. Participant attitudes about three models of consent were evaluated, including study-specific (traditional) consent [11, 12, 14, 15], broad (blanket) consent in which scope of the consent for future studies cover a comprehensive, unspecified range of topics [9, 11–15], and categorical consent in which consent is given for broad categories of research [11, 14, 15]. The source of study populations included the general public [9, 11, 12, 16] a research population [10, 13, 14], and a sample of patients at US Veterans hospitals [15]. All publications used a cross-sectional survey.

Among general public surveys which asked participants their preference for various types of consent models, most studies found that most respondents prefer to make an active decision regarding research participation. Simon et al. [11] found that more participants favor an opt-in consent approach (*actively choose to be involved*) over an opt-out approach (*actively*

Table 1 | Study characteristics

First author	Sample size (N)	Mean age (range)	Population demographics
Reconsent			
Willison et al. [9]	1230	39% age 20–39, 20% >60 years;	55% female; 33% high school or less; "younger, better educated, more likely to be women, and less likely to be single compared to Canadian pop"
Ludman et al. [10]	365	83 years (65–102)	57% female; 85% white
Simon et al. [11]	751	58.4 years	63% female; 97% white
Platt et al. [12]	4,659	18+ years	50% men / 50% women; 61% white; 16% black, 15% Hispanic; 70% less than a bachelor's degree
Kelly et al. [13]	2,308	55 years (18–87)	89% female, 11% male; UK population
Goodman et al. [14]	450	63.6 years	65% women; 95% white; 60% had bachelor's degree
Kaufman et al. [15]	931	18–75+ years	100% Veterans; 93% men; 80% white
Kaufman et al. [16]	4,659	Aged 18+ years	52% women; 70% white non-Hispanic, 11% black non-Hispanic, 12/5 Hispanic, 1% American Indian/Alaskan native
Return of results			
O'Daniel et al. [17]	100	40–49 years	73% female; 76% African-American
Murphy Bollinger et al. [18]	1,515	Aged 18+ years	53% women; 67% white non-Hispanic, 12% black, 15% Hispanic, 7% other, 29% B.A.
Middleton et al. [19]	4,961	Not detailed	Not detailed
Meulenkamp et al. [20]	1,678	55.7 /50.3 years (general vs. patient population)	57% / 55% female (general vs. patient population) 99% / 97% Dutch
Edwards et al. [21]	450	63.6 years	65% women; 95% white; 60% had bachelor's degree
Contribution to biorepository and use of de-identified data			
Kaufman et al. [15]	931	18–75+ years	100% Veterans; 93% men; 80% white
Kaufman et al. [16]	4,659	Aged 18+ years	52% women; 70% white non-Hispanic, 11% black non-Hispanic, 12/5 Hispanic, 1% American Indian/Alaskan native
Oliver et al. [22]	229	48.9 years (18–26)	58.5% female, 58.1% white/non-Hispanic, 63.7% married, 80.8% Christian, 59.2% income $40,000+, 55.8% completed at least some college degree
Goodman et al. [23]	450	63.6 years	65% female; 95% white; 60% had bachelor's degree
McGuire et al. [24]	323	48.5 years (18–86)	57.3% female, 56% non-Hispanic white, 63.7% married, 81.3% Christian, 67.8% completed at least one year college
Rahm et al. [25]	203	53.8 years (19–90)	65% female; 78% white; 84% completed beyond high school
Storr et al. [26]	1,434	29 years	58% female; 75% African American
Why participate in observational studies			
Kerath et al. [27]	1,041	40–59 years	63.7% female; 68.1% White; 63.6% married; 79.3% higher education
Porteri et al. [28]	145	47.5 years	M/F ratio: 36/109; Education 5–22 years
Soule et al. [29]	164	61.5 years	84% male; 83.5% white
Goodman et al. [30]	450	63.6 years	65% women; 95% white; 60% had bachelor's degree
Kaufman et al. [31]	4,659	Aged 18+ years	52% women; 70% white non-Hispanic, 11% black non-Hispanic, 12/5 Hispanic, 1% American Indian/Alaskan native

choose to not be involved) (67% vs. 18%), and broad consent is endorsed by more participants (41%–52%) than either a categorical consent model (10%–25%) or a study-specific consent model (29%–48%) [11, 12, 16]. When asked about consent for the use of data from medical records, a telephone survey of the Canadian population found that 32% of respondents felt that they should be asked each time, 28% endorsed giving general permission, 24% agreed with notification of use only, and 12% responded that they thought their medical records could be used without their permission and without notification [9]. The two most common reasons given for a broad consent preference were that it is easier to sign a consent only once and the research will help others by improving treatment and saving lives [11, 12]. Two general population studies have shown demographic differences in preferences for consent models. Broad consent is favored over categorical or study-by-study consent by older participants (OR

Table 2 | Summary of major findings

First author	Source of participants/Study design	Major findings
Reconsent		
Willison et al. [9]	General population/cross-sectional survey	60% felt permission necessary; 36% preferred minimal or no involvement; 24% endorsed notification process; 12% felt no permission or notification necessary.
Ludman et al. [10]	Research population/cross-sectional survey	Very (69%) or somewhat (21%) important to be asked permission.
Simon et al. [11]	General population/mixed methods (focus groups and cross-sectional survey)	67% preferred opt-in consent compared with opt-out or no consent. Broad consent preferred by more than study-specific consent or categorical consent
Platt et al. [12]	General population/cross-sectional survey	52% preferred broad consent compared with study-by-study consent. Younger participants and women less likely than men to prefer broad consent (54% men vs. 48%). Broad consent preferred by those that felt participating would "make me feel like I was contributing to society" (OR = 1.85, p = .001); accelerate medical treatments and cures (OR = 2.20, p = .001 participating would be easy (OR = 1.59, p < .001)
Kelly et al. [13]	Research population/cross-sectional survey	58% approve reconsent for studies on the initial disease by the same researcher; 44% for same researcher but different disease; 31% for different investigator and same disease; 26% for different investigator and disease. 50%–57% preferred new consent form for further use of their medical information and DNA to be used in ethics-approved research.
Goodman et al. [14]	Research population/cross-sectional survey	Participants with cancer significantly more likely to endorse reconsent to study a related condition (p < .01), unrelated condition (p < .04), or new gene (p < .002). Cases significantly more likely to favor reconsent for unrelated health conditions and a new gene compared with controls (p < .05; .01, respectively). Participants with higher stage of cancer significantly more likely to not endorse reconsent.
Kaufman et al. [15]	VA patients/cross-sectional survey	47% preferred "blanket consent"; 43% preferred separate consent for each study; 10% endorsed broad categories of consent
Kaufman et al. [16]	General population/cross-sectional survey	48% prefer consent once for all research; 42% prefer study-by-study consent
Return of individual results		
O'Daniel et al. [17]	General population/mixed methods (focus groups and cross-sectional survey)	94% would be likely to participate in a study that returned individual research results compared with one that offered to return a summary report (74%, p < .00001) versus one that did not return any results (66%, p < .00001)
Murphy Bollinger et al. [18]	General population/experimental design	56% would participate hypothetical study; 57% would want all genetic results; 56% want results for preventable/treatable disease; 84% would agree to not receiving results with tradeoff of a prefer shorter study
Middleton et al. [19]	General population/cross-sectional survey	Most participants thought it was acceptable to receive information in all categories, even if the risk of the condition occurring was low.
Meulenkamp et al. [20]	General and research population/ cross-sectional survey	66–88% "probably" or "definitely" would like results of a mutation. Information preference dependent on if treatment available; if they do or do not have the disease; the severity of the condition.
Edwards et al. [21]	Research population/cross-sectional survey	Results should be returned if researcher feels the participant might be interested in knowing (77%); individual results should be returned if results would affect a participants' health or health care (>80%); results should be returned if a participant asks for them (>50%)
Contribution to biorepository and use of de-identified data		
Kaufman et al. [15]	VA patients/cross-sectional survey	71% would definitely (22%) or probably (49%) participate in genomic database. Black non-Hispanics less likely than white non-Hispanics to participate (OR = 0.4; p = .01); Hispanics (OR = 3.4; p = .04) and those with ≥1 year college (OR = 2.4; p = .00002) more likely to participate.

(Continued)

Table 2

First author	Source of participants/Study design	Major findings
Kaufman et al. [16]	General population/cross-sectional survey	82% of those surveyed would provide a biospecimen. Black non-Hispanics, American Indians, and Alaska Natives were 60% less likely to consent to providing biospecimen compared with white non-Hispanics (p = .03). Women (84%, p = .0001), those earning > $75,000 (88%, p = .04), and those with bachelor's degree (87%, p = .009) more likely to provide biospecimen.
Oliver et al. [22]	Research population/experimental design	83.9% initially consented to public data release; 53% chose public data release after debriefing; 32.9% chose not to release data beyond study PI; Reasons for contributing included: 74% important to advance research; benefits to sharing their genetic information (72.7%); advancing research to help others with a similar condition (62.7%).
Goodman et al. [23]	Research population/cross-sectional survey	90% endorsed adding data to a research repository so that their information will be available to as many studies as possible. 20% endorsed maintaining a link to de-identified data. Reasons to maintain link included return of results (50%); support future research (50%).
McGuire et al. [24]	General population/experimental design	Most participants (84.9%) randomized to binary consent chose public data release, while the remaining individuals (15.1%) opted out of data sharing (no release). 66.4% of participants randomized to tiered consent agreed to public data release, 19.5% chose restricted release, and 14.1% chose no release.
Rahm et al. [25]	Patient population/cross-sectional survey	69% of the patient population were willing to contribute to a biorepository. 74% agreed to contribute because "it is important to contribute to research." 56% had no concerns about contributing.
Storr et al. [26]	Research population/cross-sectional survey	In a long-term cohort study, 75% donated biospecimen and 90% consented to storage and sharing. Odds of providing biospecimen decreased with less education, history of drug use, for minorities (OR = 0.37, 0.18–0.75), and former cannabis users (OR = 0.46; 0.27–0.77)
Why participate in observational studies		
Kerath et al. [27]	Health system patients and their families/cross-sectional survey	Most supportive of genetic research and those who did not approve of their genetic material being used in research concerned about privacy of personal information or extra blood drawn. Very few opposed on moral grounds. General lack of understanding about the various consent processes that go along with genetic research.
Porteri et al. [28]	Family members of patients attending visit for cognitive impairment or dementia/cross-sectional survey	Reasons to participate included an increase in knowledge (76%) and benefit to future generations (42%).
Soule et al. [29]	Cardiac patients/cross-sectional survey	Intellectual Motivation Score 7.8/10 (SD 2.3); Altruistic Motivation Score 9.0/10 (SD 1.7); Health-related Motivation Score 6.7/10 (SD 3.3); Financial Motivation Score 2.2 (SD 2.1); Other Motivations included feelings of gratitude toward team and hospital, desire to "give back," liking the researcher, interest in learning from the study, participating was the "right thing to do."
Goodman et al. [30]	Research population/cross-sectional survey	Reasons to participate included a benefit to society (99%), reputation of research institution (97%), gain information to improve personal health (75%), gain information previously didn't know (67%), financial incentive (20%).
Kaufman et al. [31]	General population/cross-sectional survey	Return of results was largest motivator for participation (OR = 1.6; p < .0001

for 10-year age increase = 1.07, p = .05) [11, 12]. In addition, one study found that women are less likely to prefer broad consent than men (OR = 0.75, p = .008) [12], and participants with an income less than $25,000/year are less likely to prefer an opt-in approach (68% vs. 81%, p = .01) [11].

Among 365 participants of a cohort study of aging and dementia, Ludman et al. [10] found that 90% of participants felt it was important or very important that they were asked their permission to participate, and most respondents felt that a notification approach or a "no communication" approach are not acceptable (67% and 70%, respectively). Others have found that participant attitudes vary by investigator, disease studied, and participant demographics. Kelly et al. [13] found that among 2,308 UK twin

registry volunteers, 58% of respondents agreed that reconsent was not necessary if their data was to be used for further studies on the same disease by the same investigator. Most participants preferred to be reconsented when a new study focused on an unrelated health condition or when sharing data or samples with researchers at a different institution [13, 14]. Participants also felt that notification alone was sufficient when the new research involved a different gene but the same type of cancer [8]. Reasons given for endorsing a reconsent model if the new study involves a different investigator and different disease include wanting to know who will have access to their data (65%), wanting to have control over their own data (54%), and concern about their privacy (30%) [13]. Women, younger participants, and those with a history of cancer were significantly more likely to request reconsent [13, 14].

Return of genetic results

Six studies investigated participant views about the return of individual genetic research results among the general population [17–20] and a research population [20, 21]. One study employed an experimental design [18] and the remainder used a cross-sectional design.

Cross-sectional studies found that the return of individual genetic results was overwhelmingly desired by respondents from both the general population [17, 19, 20] and research study participants [21, 22]. For example, Middleton et al. [19] found that among 4,961 English-speaking internet users from 75 countries, nearly all participants favored receiving information about life-threatening, preventable, genetic diseases, and the trend to receive genetic information decreased as the severity of the disease diminished. An experimental design study among 1,515 U.S. adults was conducted to measure the types of genetic research results desired by the general population and found that while 78% of respondents would like their individual results returned, 57% preferred the return of all their genetic results and 32% favored results for preventable or treatable diseases [18]. Meulenkamp et al. [20] demonstrated that among both the general population and the research population in the Netherlands, 58% of respondents favored receiving individual genetic results, even if there were no results that *showed no genetic mutation*. Finally, among a group of 450 research participants, 77% expressed a desire to have results returned to them if the researcher believed the participant might be interested in knowing them, if the results would affect a participants' health or health care (>80%), or if a participant asks for them (>50%) [21].

Contribution of data to a biorepository and use of de-identified data

Of the seven publications in this review which examined the contribution to a biorepository and the use of de-identified data, five were cross-sectional and two were experimental.

Cross-sectional studies found strong support for the addition of data to a biorepository among the general population [16], a group of veterans [15], patients [25], and research participant groups [23, 26], with willingness to donate data to a biorepository ranging from 69% [25] to 90% [23]. Agreement for genomic data sharing was also shown in an experimental design study. Among a group of 229 research participants, most felt that the benefits of genomic data sharing outweigh the risks, with 72.7% strongly agreeing and 25.1% agreeing that there are benefits to data sharing [22]. The most important factors influencing the decision to agree to contribute to a biorepository included wanting their data to be available for as many studies as possible, thereby increasing their chance of receiving personal health information (90% of respondents) [23], feeling that the contribution is important for research (74% of respondents) [25], advancing research to help others (62.7% of respondents), and advancing general medical knowledge (23%) [22]. In a randomized trial designed to compare the effect of three different consent documents (traditional, binary, and tiered) on data sharing choices, McGuire et al. [24] found that, overall, respondents were more likely to approve public data release (data available both publically and with access limited to approved researchers only) compared with restricted data release (release of genetic information into a restricted database, available to approved researchers only) (53.1% vs. 33.1%).

Demographic differences in views related to contribution to a biorepository have been shown in several studies [15, 16, 25]. Willingness to provide a biospecimen was associated with increased age (OR = 2.73; 1.10–6.76) [25], income (88% agreement to contribute among those earning more than $75,000/year; p = .04) [16], and education (87% agreement to contribute among those with a bachelor's degree, p = .009 [16] or those with one or more years of college (OR = 2.4, 95% CI 1.4–3.9) [15]). Compared with non-Hispanic whites, black non-Hispanics (p = .0005) and American Indians and Alaska Natives (p = .03) have been shown to be less likely to agree to contribute [16], while Hispanics are more likely to contribute to a biorepository (OR = 3.4, 1.0–11.3) [15]. Demographic differences have also been shown regarding data release preferences. Hispanics were less likely to choose public compared with restricted data release (OR = 2.94; CI 1.16–7.43) or no release (OR = 3.94; CI 1.05–1.76) [25]; unmarried participants (OR = 2.40 CI 1.05–5.44) and those with some college (OR = 3.52; CI 1.02–12.14) or a college degree (OR = 4.67; CI 1.35–16.12) were more likely to choose a restricted compared with a public data release [24].

Results of both a cross-sectional study and a randomized trial of consent for data sharing found that

over 50% of respondents were not concerned about being personally identified when participating in a genetic study that used de-identified data [23, 24]. However, support was relatively low for maintaining a link between the research participant and de-identified data, with only 20% of respondents expressing that a link should not be maintained [23]. Reasons participants cited for maintaining a link included allowing for the return of personal health results (50%) or to support future research by allowing contact for additional information (50%) [23]. Participants felt it was more important to advance research rather than protect privacy when contributing to a public (56.8% vs. 31.3%) but not restricted (37.1% vs. 42%) databank [24]. Only one study found that older participants were significantly less likely to believe that no link should be maintained between their identity and their de-identified data (RR = 0.97; 95% CI = 0.94–0.99), while participants with cancer at baseline were significantly less likely to prioritize the maintenance of a link to de-identified data to allow participation in future studies rather than obtaining personal health information (RR = 0.58; 95% CI = 0.38, 0.90) [23].

Motivation for participation in observational studies

Five quantitative studies were included in the review of factors motivating participation in observational genetic studies [27–31]. All studies were a cross-sectional design.

Among the general population, the return of genetic results was closely tied with motivation to participate in research studies. Kaufman et al. [31] found that the return of results is the largest motivator for participation, increasing willingness to participate by 6% (OR = 1.6; $p < .0001$), and the likelihood of participating increased from 66% with no individual results given to 94% if individual genetic results are provided ($p < .00001$) [17]. Results of an online cross-sectional survey of 4,659 U.S. adults found that the return of individual genetic results was the largest motivator for observational study participation (OR = 1.6; $p < .0001$), followed by compensation (OR = 1.5; $p < .0001$) and lowering study burden (OR = 1.2; $p < .01$). Lowering the study burden was significant among women but not men, and increasing compensation was the strongest motivator in households with incomes <$25,000 per year or >$75,000 per year [31].

A recent study in research population of cancer patients, controls, and family members found that factors that motivated respondents to participate in genomic research included a benefit to society (99%); the reputation of the research institution (97%); gaining personal information that may improve their personal health (75%); and gaining information they did not previously know (67%). Only 20% of participants viewed financial incentives as a motivator for research participation. Participants with cancer endorsed the personal meaningfulness of research as a factor for participation in research compared with participants without cancer (OR = 0.61, 0.42–0.89; OR = 0.62, 0.42–0.91), and those with a more advanced stage of cancer were significantly more likely to participate in research because they felt that the research could benefit their family (OR = 2.72, 0.99–7.50). While all cases were significantly more likely to feel that the research must be meaningful to them personally compared with controls (OR = 1.56, 1.05–2.34), women were 50% more likely than men to believe that a family benefit is an important determinant of research participation (OR = 1.73, 1.16–2.58) [30]. In a patient and family population, 5.7% did not approve of participating in a genetic research study and reported concern about the security of their personal information (75.3%), concern about having an extra tube of blood drawn (14.3%), and expressed that their participation was interfering with nature (10.3%) [27]. Among 164 hospitalized cardiac patients, Soule et al. [29] found that altruistic motivation ranked highest regarding reasons for study participation; however, a subgroup of patients with a lower comorbidity index score were more likely to endorse participation citing interest in the study and research question. Lastly, family members of patients with cognitive impairment or dementia reported that the major reason for participating in genomic research was to increase knowledge (76%) and benefit future generations (42%) [31].

Discussion

This review summarizes participant preferences and highlights potential differences by demographics and participant population which should be considered while implementing future observational genomic studies such as the All of Us Research Program. Incorporating participant perspective in these large observational studies is important for two categories of reasons. One, it may improve the conduct of the studies by reducing burden on participants. Second, it may improve participation rates and yield for studies like the ones reviewed.

Reconsent and broad consent

While the large majority of participants find participation in research and the addition of their personal information to a shared databank acceptable, most studies found that participants express the importance of giving direct consent to retain personal autonomy [32]. The traditional informed consent, that is, a contract between a singular research team and research participant to study a single exposure-disease association, is technically challenging in many current and future research environments.

Broad consent, or the consent to use data and samples for future, non-specified studies, was supported by both general and research population-based

studies; however, many preferred the option to select the broad categories of research, for example, disease categories (e.g. cancer, cardiovascular disease, diabetes) or methodology categories (e.g. genetic analysis, medical record review) [11]. Additional variations to the consent model were proposed in a few studies, including categorical and study-specific consent. In two general population surveys, one reason cited for preferring broad consent is that it is less burdensome [11] and participants would feel less "bothered" [12] compared with study-by-study consent. Further research is needed to understand research participant preferences to these largely new models of consent and whether this perceived lower burden translates into increased research participation and retention rates.

Quantitative studies which have examined participant views regarding reconsent have uniformly found an underlying importance of trust related to the likelihood of participant acceptance of alternatives to the traditional study-by-study consent. Some of these studies were conducted among the general population [9, 11, 12]. Many, however, included participant groups with long-standing researcher–participant relationships, and yet most participants still favored notification and/or reconsent prior to the addition of their data to a shared data set [10, 13, 14]. Significant differences have been shown by gender and age, with women and younger participants significantly less likely to endorse reconsent [13, 14]. It is critical to understand the demographic make-up of the population from which future large longitudinal cohorts will be recruited so that strategies may be tailored to address demographic-specific concerns and participants desire for control over research participation. By increasing trust and diligently informing participants, while being sensitive to the participants' time, researchers may increase the acceptability of alternative models of reconsent and broad consent.

Return of individual genetic results

The application of whole exome and genome sequencing in population-based research has introduced the availability of a tremendous amount of genetic data, including genetic information associated with rare and common diseases, medication safety and efficacy, non-health-related information, as well as incidental information for which we do not, yet, understand the significance. The research community, however, is divided about the return of some or all the individual genetic results produced from research, or which categories of genetic results should be returned to research participants. Reasons cited in favor of the return of genomic results include the value of the genetic information, respect of the participant, and increased participant autonomy [33]. Alternatively, those who oppose the return of individual results argue that the goal of research is the advancement of knowledge, not the treatment of individual patients [34]; the original intent of the participant was altruistic [35]; harm may come from disclosure of non-validated results [35] and there is a chance for "therapeutic misconception"—or the confusion between research and clinical results [36]; return of individual results may be perceived as undue inducement to participate [36]; and concern for legal liability [37]. Finally, budgets and duration of funding often do not cover the additional time and resources necessary to return individual results [38].

Quantitative studies, both population-based and those of existing research participants, have confirmed that participants highly endorse the return of individual genomic results and that the return of results is associated with their motivation to participate in research. Goodman et al. [23] found that 80% of research participants felt that an important reason to contribute their data to a research repository was to gain personal health information. In order to fully understand this issue, we may need good mixed methods studies, where survey data are combined with qualitative explorations to see the complete picture.

While it has been suggested that the return of individual genetic results may increase trust and improve recruitment, it is also possible that by providing potential participants with additional details and information about tradeoffs of returning results versus more or faster research, they may make different choices. Although it has been shown that only about one-third of research participants are able to correctly answer a question about the study's aim [39], one study demonstrated that when participants were educated regarding the increased cost and/or time required to complete a study if individual genetics results were returned, 84% of respondents preferred a study that did not return individual results if it was completed in a shorter timeframe [18].

Contribution of data to a biorepository and use of de-identified data

The attitude of research participants regarding the addition of their data to a data repository is favorable and it appears that most participants, including both public and research populations, positively view the benefits of combining and sharing data to strengthen the scientific usefulness of information.

The goal of de-identifying data, the removal of all personally identifiable information prior to the addition into a shared data set, is to protect the privacy of the participant. It has been shown, however, that re-identification is possible with as few as 30–80 statistically independent single nucleotide polymorphisms [39] or from pooled DNA data [40]. Most participants in these quantitative studies did not feel it was necessary to maintain a link to their de-identified data. If a link was kept, however, participants expressed the importance of research compared

with the protection of their privacy as a reason for maintaining the link. It is unclear whether participants truly are not concerned about their privacy when participating in research, do not understand the risks or possibility of a breach of privacy, or are willing to accept the risk of re-identification for the greater good. What is clear, however, is that until additional privacy measures are created and implemented, participants need to fully understand the risks involved with data sharing and that de-identifying genomic data does not eliminate those risks.

Motivation for participation

Although overall research participation rates have declined recently [7], there appears to be widespread overall public support for large, prospective observational studies to evaluate genes and the environment [31, 41]. The reasons given for joining research studies varied by population source. The return of individual genetic results is the strongest motivator for participation among general population studies. In research-based populations, altruism, an increase in knowledge, and the reputation of the research institution were the strongest motivator and gave incentives much less importance in their decision to participate. It is interesting that the general population weighed incentives as the second most important factor influencing their decision [31] and yet only 20% of the research population felt this was a motivating factor [30]. It has been proposed that altruism in research participation is associated with the ratio of risks to benefits [42]. It is possible that the general population may perceive this ratio to be greater than an experienced research population.

Limitations of this review

It is possible that differences in participant views presented in this review result from the varied source from which the participants were recruited. These quantitative studies include participants from both population-based surveys and research participants currently enrolled in registries or longitudinal studies. Differences between those who agree to participate in a research study compared with those who do not choose to enroll as a study participant may fundamentally view the concept differently. The research participant group may be biased in that it excludes the views of those who chose not to participate. Alternatively, the correlation between respondents that, presented with a hypothetical study, report they *would* participate and those that *actually* participate is not good [31], influencing the results from the general population surveys. In addition, the experience of being a research participant may impact their views related to consent, sharing data, and the return of results. Participants from the general population were typically younger than registry or current study participants and the majority of research population-based studies included predominantly educated, non-Hispanic whites. Because the principle aim of these studies was to quantitate participant views, it is unlikely that publication bias was present.

Limited research has been done on participant views regarding genomic observational studies, as indicated by our identification of only 23 quantitative publications which met our criteria. As a result, there are inconsistent key words resulting in missed relevant literature. It is possible that this review may have not included all pertinent studies.

CONCLUSION

The success of the future observational genomic studies, including the All of Us Research Program, is dependent, in part, on public support. Recruitment of diverse participants is crucial to minimize non-participation bias, reduce errors in inferences between the research cohort and general population, and allow for a representative study population. To date, however, few studies have included minority populations and more research is needed to understand potential differences in research participant concerns regarding enrollment in longitudinal genomic studies by race/ethnicity.

There is much that still is not known about participant views. For example, further research is needed to appreciate the level of participant understanding regarding important topics such as incidental genetic findings, the advantages and disadvantages of de-identifying data, and maintaining a link to de-identified data. While quantitative studies help identify patterns in participant viewpoints, additional mixed methods and qualitative studies are necessary to help understand the beliefs which determine participant perspectives and to inform guidelines for observational genomic research.

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Compliance with Ethical Standards

Conflict of Interest These authors do not have actual or potential conflicts of interest.

Primary Data Findings reported in this article have not been previously published and the manuscript has not simultaneously been submitted elsewhere. There are no previous reports of these data. The authors have full control of all primary data and agree to allow the journal to review these data, if requested.

Study Approval The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. This study did not involve research animals. IRB approval was obtained from all participating institutions.

Informed Consent All research participants provided written, informed consent.

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