What should be included in Informed Consent for GRoR?

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Disclosures

- Vice Chair of the IRB for the All of Us Research Program
- Views expressed are not the views of the program or the IRB

Interrelated but distinct

- What is to be returned?
  - The minimal ethically required?
  - Nearly all possible information?
  - Health related findings only? PGx?
  - Ancestry? Recreational findings?
- What is disclosed about what is returned ?
- What is to be disclosed about what research is to be conducted
  - Broad consent covering future uses
  - Tiered consent distinguishing different disease states
  - Specific consent for uses of data

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ARTICLE

Return of Genomic Results to Research Participants: The Floor, the Ceiling, and the Choices In Between

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Consensus Statement

- Floor— “At a minimum… researchers should offer individual genomic research results that are valid, medically important, and actionable if discovered purposefully or by chance during the course of data analysis.”
- The ceiling-– “Researchers might be ethically and scientifically justified in returning all genomic information… in some format…”
- In between---might also be justified in offering something in between “all actionable results identified during research” and “all genomic information”

PLOS ONE

RESEARCH ARTICLE

Return of individual research results from genomic research: A systematic review of stakeholder perspectives

Danya F. Vears[1,2,3,4]*, Joel T. Minion[5,6], Stephanie J. Roberts[5], James Cummings[7], [5] [9] Lorraine Cowley[10,11]

"We found overwhelming evidence of high interest in return of IRR from potential and actual genomic research participants. There is also a general willingness to provide such results by researchers and health professionals, although they tend to adopt a more cautious stance. While all results are desired to some degree, those that have the potential to change clinical management are generally prioritized by all stakeholders. Professional stakeholders appear more willing to return results that are reliable and clinically relevant than those that are less reliable and lack clinical relevance. The lack of evidence for significant enduring psychological harm and the clear benefits to some research participants suggest that researchers should be returning actionable IRRs to participants."

Consent options

- Specific consent often not an option for scientifically useful research repository of a general nature
- Broad consent— “In general, broad consent is preferable whenever possible to facilitate future research and increase the scientific value of the data.” (HHS Guidance 2019)
- Tiered consent –divide by test and disease characteristics
- Could also create tiers of return of results

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ARTICLE

A tiered-layered-staged model for informed consent in personal genome testing

Eline M Bunnik*,[1], A Cecile JW Janssens[2] and Maartje HN Schermer[1]

In recent years, developments in genomics technologies have led to the rise of commercial personal genome testing (PGT): broad genome-wide testing for multiple diseases simultaneously. While some commercial providers require physicians to order a personal genome test, others can be accessed directly. All providers advertise directly to consumers and offer genetic risk information about dozens of diseases in one single purchase. The quantity and the complexity of risk information pose challenges to adequate pre-test and post-test information provision and informed consent. There are currently no guidelines for what should constitute informed consent in PGT or how adequate informed consent can be achieved. In this paper, we propose a tiered-layered-staged model for informed consent. First, the proposed model is tiered as it offers choices between categories of diseases that are associated with distinct ethical, personal or societal issues. Second, the model distinguishes layers of information with a first layer offering minimal, indispensable information that is material to all consumers, and additional layers offering more detailed information made available upon request. Finally, the model stages informed consent as a process by feeding information to consumers in each subsequent stage of the process of undergoing a test, and by accommodating renewed consent for test result updates, resulting from the ongoing development of the science underlying PGT. A tiered-layered-staged model for informed consent with a focus on the consumer perspective can help overcome the ethical problems of information provision and informed consent in direct-to-consumer PGT.
European Journal of Human Genetics (2013) **21,** 596–601; doi:10.1038/ejhg.2012.237; published online 21 November 2012

Table 1 A proposed contents of the first layer of the information provision process

	Information elements	*Examples*
1	Purpose of the test	Prediction of disease risks Provision of information on carrier status for reproductive decision-making Education/information Entertainment
2	Target group	Adult consumers without health problems or positive family history Couples planning to conceive
3	Limitations	Probabilistic *versus* diagnostic information Test results may change over time
4	Implications and risks	Psychological implications (eg anxiety) Medical implications (eg unnecessary follow-up) Social implications (eg insurance) Implications for family members
5	Tiers	Non-medical tests Medical tests of limited *versus* high clinical validity and utility Medical tests subdivided into categories (tiers) of diseases tested for according to disease characteristics (eg severity, age of onset)
6	Follow-up	Follow-up testing and diagnostic workup for clinically actionable test results
7	Data protection	Access by third parties (eg researchers)
8	Sources of independent information	Links to government/consumer/patient organisation websites

- Tiered vs Broad Consent (plus element of open data sharing) had no impact likelihood to participate

ARTICLE

Public Attitudes toward Consent and Data Sharing in Biobank Research: A Large Multi-site Experimental Survey in the US

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CONTRIBUTORS

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Recommendation 6: Include Plans for the Return of Individual Research Results in Research Protocols.

For all studies using human biospecimens, investigators should routinely address their plans regarding the return of individual research results in their funding application or research protocol. The investigator's plan should describe

A. whether individual research results will be offered to participants and, if so, when and how. The plan should also provide the rationale for these decisions, including how participant needs, preferences, and values were considered;
B. how the consent process will reflect transparency and effective communication with participants regarding whether and, if so, how individual results will be offered;
C. how investigators and their institutions will respond if participants request their results, including how information in the designated record set will be released to participants when they have a right to access their individual research results under HIPAA; and
D. the budget and resources for the return of individual research results, when appropriate.

Recommendation 9: Ensure Transparency Regarding Return of Individual Research Results in the Consent Process.

In the consent process, investigators should communicate in clear language to research participants

A. which individual research results participants can access, if requested, including any results participants have a legal right to access under HIPAA, and how to request these results; and

B. which individual research results, if any, will be offered to participants and why, and the participant's option to decline to receive their research results.

C. If results are going to be offered the following elements should also be communicated during the consent process:

1. the risks and benefits associated with receiving individual research results;

2. conditions under which researchers will alert participants of urgent results

3. at what time and through what process results will be communicated to participants;

4. whether the results will be placed in the participant's medical record and whether the results will be communicated to the participant's clinician; and

5. when relevant to the research protocol, the participant's option to have results shared with family members in the event the participant becomes incapacitated or deceased

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ESHG

ARTICLE

Check for updates

Return of individual genomic research results: are laws and policies keeping step?

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Numerous national laws [24;28] and policies [30;32;39;40;41] therefore recommend or require participants be informed of the return policy during the consent process before consenting. Denmark's genomic research guidelines require pre-test counselling for the study of highly penetrant genes, and recommend consent include an estimate of the frequency of incidental findings [33].

Other norms extend beyond providing information, and encourage or require researchers to offer participants a choice about receiving results (e.g., an opt-in or opt-out) [4;10;29;31;37;38;42–45]. The CIOMS/WHO guidelines go further and recommend offering participant tiered choices [8]. Australia's health research guidelines even expect participants to have opportunities to update their preferences about the return of results

Table 3 Final round results (n = 47)

	Adequate comprehension?[a] *n* (%)		
		Disagree[b]	
Consent form topic	**Agree**	**Too little**	**Too much**
Biobank purpose: "The purpose of this project is to collect and store samples and health information for use in future research."	41 (87)[c]	6 (13)	0 (0)
Blood draw: "You are going to draw blood from me."	35 (74)[c]	12 (26)	0 (0)
Collection of information: "You will ask me some basic information and will contact me to update this information. You will also collect information from my medical records."	46 (98)[c]	1 (2)	0 (0)
Duration of storage: "My sample and information will be stored forever unless I decide to stop taking part."	46 (98)[c]	0 (0)	1 (2)
Access to biospecimens/data: "Researchers may study my samples and information. You will not give researchers information that could identify me."	35 (74)[c]	11 (23)	1 (2)
Recontact: "Someone from the biobank may contact me about participating in additional research."	41 (87)[c]	5 (11)	1 (2)
Large-scale data sharing: "Some of my information might be put into a database. There is a small chance that someone could trace my information back to me."	39 (83)[c]	5 (11)	3 (6)
Risks: "There is a risk that someone could get access to information about me."	33 (70)[c]	11 (23)	3 (6)
Confidentiality protections: "You will take many steps to protect my privacy."	43 (91)[c]	2 (4)	2 (4)
Genetic Information Nondiscrimination Act: "There is a law against discrimination based on my information."	28 (60)	12 (26)	7 (15)
Alternate: There is nothing in this section a prospective participant must understand to give valid consent.	25 (53)	NA	NA
Certificate of confidentiality: There is nothing in this section a prospective participant must understand to give valid consent.	36 (77)[c]	NA	NA
Potential benefits: "I should not expect to benefit from this research."	45 (96)[c]	1 (2)	1 (2)
Costs and payments (commercialization): "I will not get money from anything that is done using my sample."	43 (91)[c]	3 (6)	0 (0)
Return of results: "I should not expect to get individual results back from this research."	40 (85)[c]	6 (13)	0 (0)
Discontinuing participation: "I have the right to leave the project. However, I cannot withdraw or get back samples and information from studies that have already begun."	41 (87)[c]	2 (4)	4 (9)
Questions or problems: "There is someone I can contact if I have questions or want more information."	46 (98)[c]	0 (0)	0 (0)

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Informed consent for biobanking: consensus-based guidelines for adequate comprehension

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Table 3 Participant characteristics by need for review/retest (weighted)

	Required review and retesting		
	No (*n* = 374)	Yes (*n* = 1,542)	
	n (%)	*n* (%)	*P* value*
Consent form			
Simplified form	189 (51)	780 (51)	0.98
Traditional form	185 (49)	762 (49)	
Age group[a]			
18–29	41 (11)	164 (11)	0.04
30–44	124 (33)	414 (27)	
45–59	114 (31)	476 (31)	
≥60	96 (26)	488 (32)	
Education[a]			
Less than high school	11 (3)	232 (15)	<0.0001
High school	63 (17)	423 (27)	
Some college	129 (35)	433 (28)	
Bachelor's degree or higher	172 (46)	454 (30)	
Race/ethnicity			
White, non-Hispanic	312 (83)	999 (65)	<0.0001
Black, non-Hispanic	15 (4)	197 (13)	
Other, non-Hispanic	8 (2)	66 (4)	
Hispanic	20 (5)	234 (15)	
Two or more races, non-Hispanic	19 (5)	45 (3)	
Sex			
Male	182 (49)	715 (46)	0.49
Female	192 (51)	826 (54)	

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Improving biobank consent comprehension: a national randomized survey to assess the effect of a simplified form and review/retest intervention

Laura M. Beskow, MPH, PhD[1,2], Li Lin, MS[1], Carrie B. Dombeck, MA[1], Emily Gao, BA[1] and Kevin P. Weinfurt, PhD[1,3]

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Target Article

Check for updates

Exploring Understanding of "Understanding": The Paradigm Case of Biobank Consent Comprehension

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"Within the context of biobanking consent, we previously convened a multidisciplinary panel to reach consensus about what information must be understood for a prospective participant's consent to be considered valid. Subsequently, we presented them with data from another study showing that many U.S. adults would fail to comprehend the information the panel had deemed essential. When asked to evaluate the importance of the information again, panelists' opinions shifted dramatically in the direction of requiring that less information be understood. Follow-up interviews indicated significant uncertainty about defining a threshold of understanding and what should happen when prospective participants are unable to grasp key information."

All of Us Research Program—a success story and a precautionary tale

- Program had problem of building an airplane while it is in the air
- IRB had the problem of reviewing a program where that would be the case
- In ideal world, full GRoR plan would have been part of initial protocol, consent information and forms would have included those plans from the beginning, prior to recruitment
- In practice, not what happened
  - Earliest participants who signed up had no mention of genetic or genomic testing
  - Some information given about plan to do testing to a small second cohort—was it sufficient to begin sequencing prior to GRoR plan?
  - Both required reconsenting
  - Developed outstanding modular approach to consent and plan about what to return --several years into the program

Controversial issue

- Do you need to include plan and info on GRoR at time of initial consent or only prior to actual return? Can you have a basic consent, allow sequencing, and then further consent when research results are ready to be returned? If so, how much information needs to be included in basic consent?

- IRB wanted detailed GRoR plan (even if prior to FDA approval and would require some changes)

Consent Materials

- Primary Consent
- GRoR Consent
- Specific Informing loops (informed consent modules) for different types of genetic information (health related and PGx sequencing results; ancestry genetic testing; recreational genetic results from genotyping).

Revised Primary Consent

- We will study your samples, including your DNA. We may measure things that naturally occur in our bodies, like cholesterol. We may look for signs of outside factors that affect health. For example, we may look for environmental toxins, medicines, or drugs.
- We will also study your DNA. DNA is in your blood and other samples.
- All human beings share more than 99% of their DNA with each other. The tiny bit that is different is part of what makes each of us unique. Things like our hair color and eye color depend on the bits of DNA that are different between human beings. We call these our DNA changes. These DNA changes can also tell you about your health and how your body works. They can tell you about where your ancestors may be from. We are still learning about what role DNA plays in many parts of our lives.
- DNA is passed from parents to kids. Half of your DNA came from your mom and half came from your dad. If you have kids, each of them will get half your DNA. In this way, your DNA also tells you about your family.
- **We will use many methods to study your samples. For example, we might study your DNA using whole genome sequencing. Whole genome sequencing is a way of studying nearly all of a person's DNA. Every person's whole genome sequence is different. It is unique to them, like a fingerprint.**
- Because All of Us will last for ten or more years, some of the methods we will use may not even be invented yet.

- **We will create a scientific database**. The scientific database will have individual-level data and samples. This includes your DNA data. Access to this database will be controlled. Researchers will have to be approved by *All of Us* to use this database. They will have to have special training before they can be approved. Their research may be on nearly any topic. They may look for patterns in DNA. This may help them discover different ways that DNA affects people. These researchers may be from anywhere in the world. They may work for commercial companies, like drug companies. They may be citizen or community scientists. Citizen and community scientists are people who do science in their spare time.

- **Researchers can also ask to study your samples or DNA directly.** We may send them a small amount of your samples or DNA so that they can do this. Before we send researchers your samples or DNA, they will have to take special training and sign a contract stating that they will not try to find out who you are. They will have to tell us what they want to study. *All of Us* will have to approve it.

- Researchers will use many methods to study your samples and DNA. Because *All of Us* will last for ten or more years, some of the methods may not even be invented yet. The data researchers get from studying your samples and DNA may be added to the *All of Us* scientific database.

What are the risks of letting you use my DNA for research?

Your DNA is a type of private information. It is unique to you.

If there is a data breach, someone could see or use your DNA information without permission. There is a very small chance they could figure out who you are. They could try to use information about your DNA against you. It could impact your employment, insurance, or family relationships.

There are federal laws that can help protect your privacy. Some of these laws say that employers can’t treat people differently because of their DNA. These laws do not apply to employers with fewer than 15 employees. These laws also say that health insurers can’t use DNA information to change your coverage, drop you, or charge you more.

Are there any benefits?

All of Us is not medical treatment. It is a research program. You will not get direct medical benefits from taking part in *All of Us*.

That said, you may indirectly benefit from taking part in *All of Us*. For example, we will provide ways for you to get access to all the data you share with us and some of the results about you. This information may be interesting to you. You may learn about your health. You may learn about your DNA changes. You will be able to share your *All of Us* information with your healthcare provider if you choose. You will have the option to learn about additional study opportunities. Finally, you will be helping researchers make discoveries that may help future generations.

Will I find out the results of the research?

Sometimes, we will ask you if you want us to check your data or samples for results that you might find interesting. For example, we may ask you to fill out another form where you can choose if you want us to check your DNA for certain kinds of DNA changes and return your results to you. This form is called the Consent to Receive DNA Results. It will tell you about the risks and benefits of having us check your DNA and about learning your results. We will not check for these kinds of DNA changes until you make a decision.

Some of the results we give you may tell you about your health and others may not.

GRoR Consent

What are “DNA changes”?

All human beings share more than 99% of their DNA with each other. The tiny bit that is different is part of what makes each of us unique. Things like our hair color and eye color depend on the bits of our DNA that are different between human beings. We call these our DNA changes. We know what some DNA changes mean, but we still have a lot to learn. For example, we are still learning what role DNA plays in most health conditions. In fact, that’s one of the reasons we are doing the *All of Us* Research Program. But for a small number of things we already know a lot about the role DNA plays.

We know that certain changes in our DNA can affect our health. For example:

- Certain DNA changes can increase our risk for a few specific health conditions. This could include some cancers and types of heart disease.
- Certain changes in our DNA can increase the risk of passing specific health conditions onto our children, even if we don’t have those conditions.
- Certain changes in our DNA can impact how a few specific medicines work.

We also know that other changes in our DNA can tell us about things like:

- Where our ancestors may be from.
- How our bodies work.

The more we study our DNA, the more we will learn what DNA changes mean about us.

GRoR consent sections

- How will you check my DNA?
- How long will it take to get results?
- What exactly will you check for?
- What will you tell me?
- Do I need to pay to get my DNA results?
- How could learning my DNA results help me?
- What are the risks of learning my DNA results?
- What are the risks of sharing my DNA results?

GRoR consent sections

- What are the limits of *All of Us* DNA results?
- Are there ways that DNA results cannot be used?
- Will you ever give out my DNA results?
- Do I have to learn my DNA results?
- When will my consent expire?
- Who can answer my questions?

Would you like to learn any of your DNA results?

☐ **No, I do <u>not want</u> to learn about any DNA results.**

- I know I can change my mind later.
- I know this means that researchers can still use my DNA to make discoveries unless I withdraw (quit).

☐ **I'm not sure right now.**

- I know that until I decide, I **<u>will not</u>** learn about any of my DNA results.
- I know I can change my mind later.
- I know this means that researchers can still use my DNA to make discoveries unless I withdraw (quit).

☐ **Yes, I <u>want</u> to learn some or all of my DNA results.**

- I know *All of Us* will ask me later what specific types of DNA results I want. I get to choose.
- I know this means *All of Us* will tell me the kinds of results I choose to learn.
- I know this means I have to keep my contact information in *All of Us* up-to-date so that you can give me my results.
- I know this means that researchers can still use my DNA to make discoveries unless I withdraw (quit).

Informing loops with more details

- Ancestry testing
- Recreational genetic tests
- Health related results of sequencing (ACMG pathogenic variants)
- PGx

Take home lessons

- Better to have plan in place and consents in place at time of protocol review
- Staged and tiered consent (with some broad consent elements) can work
  - Primary consent that includes basic info
  - Return of results specific consent that covers broad range of results to be returned
  - Specific informed consent modules for different types of results to be returned (informing loops in AoURP parlance)
- Skepticism about understanding even with outstanding approach to disclosure