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Informed Consent for Return of Incidental Findings in Genomic Research

Paul S. Appelbaum, MD[1], **Cameron R. Waldman, BA**[2], **Abby Fyer, MD**[1], **Robert Klitzman, MD**[1], **Erik Parens, PhD**[2], **Josue Martinez, BA**[3], **W. Nicholson Price II, JD, PhD**[4], and **Wendy K. Chung, MD, PhD**[3,5]

[1]Department of Psychiatry, Columbia University Medical Center and NY State Psychiatric Institute

[2]The Hastings Center, Garrison, NY

[3]Department of Pediatrics, Columbia University Medical Center

[4]Petrie-Flom Center for Health Law Policy, Biotechnology, and Bioethics, Harvard Law School

[5]Department of Medicine, Columbia University Medical Center

Abstract

Purpose—Researchers face the dilemma of how to obtain consent for return of incidental findings (IFs) from genomic research. We surveyed and interviewed investigators and study participants, with the goal of providing suggestions for how to shape the consent process.

Methods—We performed an online survey of 254 US genetic researchers identified through the NIH RePORTER database and abstracts from the 2011 American Society of Human Genetics meeting; and qualitative semi-structured interviews with 28 genomic researchers and 20 research participants.

Results—Most researchers and participants endorsed disclosure of a wide range of information about return of IFs, including: risks, benefits, impact on family members, data security, and procedures for return of results in the event of death or incapacity and for recontact. However, most researchers were willing to devote 30 minutes or less to this process, and expressed concerns that disclosed information would overwhelm participants, a concern shared by many participants themselves.

Conclusion—There is a disjunction between the views of investigators and participants about the amount of information that should be disclosed and the practical realities of the research setting, including time available for consent discussions. This strongly suggests the need for innovative approaches to the informed consent process.

Keywords

informed consent; incidental findings; return of results; genome sequencing; benefits and risks

Corresponding author: Paul S. Appelbaum, MD, NY State Psychiatric Institute, 1051 Riverside Drive, Unit 122, New York, NY 10027; (p) 212-543-4184; (f) 212-543-6752; psa21@columbia.edu.

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Whole genome and whole exome sequencing are becoming prevalent tools in medical research.(1) Given the nature of the resulting data, it is possible to identify a variety of genetic findings for most participants unrelated to the primary focus of the study--commonly referred to as “incidental findings” (IFs).(2) IFs in genomic research vary in predictive power; severity of the conditions to which they predispose; degree to which those conditions can be prevented or treated (“clinical actionability”); extent to which persons may choose to modify their behavior in response; and intrinsic interest for potential recipients.(3) As genetic knowledge increases, the likelihood that IFs can be accurately identified will grow as well.

Researchers, regulators, and ethicists have struggled with how to respond to the potential for genomic research to produce IFs. Studies of participants’ preferences have found consistent interest in knowing about IFs, especially if clinically actionable.(4–8) In keeping with these preferences, a growing number of federal agencies, expert panels, and authors have recommended that at least some genomic IFs be made available to participants. Although there are substantial differences among these recommendations, there is general consensus that data should be offered when they have clear implications for helping participants make healthcare decisions, with somewhat less agreement about data for life-planning choices.(3,9,10–13) However, dissenting positions exist, especially within the research community, where concerns about the feasibility and cost of analyzing and returning IFs are often voiced.(2,4,14–16)

Although how genomic IFs ultimately will be dealt with is not completely clear, assuming continuing consensus that at least some findings should be returned to participants, the question of how best to obtain informed consent for return of IFs must be addressed. Expert guidelines (3,9,10) concur that participants’ preferences should be ascertained in the consent process, and federal regulations on protection of human subjects (“the Common Rule”)(17) appear to require disclosure of foreseeable benefits and risks of receiving IFs when they will be made available.(18) Other legal duties may also shape researcher obligations to obtain informed consent regarding return of IFs, though law in this area is developing slowly.(18,19) However, there are a number of challenges in the consent process. Investigators prospectively discussing the return of genomic data with participants will not know the likely findings for any specific participant. Hence, the benefits and risks of receiving such data and other relevant information (e.g., potential implications for family members) will need to be framed in general terms.

Given that the consent process is already time-consuming, with consent forms much longer and more complicated than most research subjects can read or absorb (20,21), whether potential subjects can attend to even longer disclosures, written or verbal, including options for return of IFs, is highly uncertain. Ascertaining which information is crucial to participants’ decision making and which can be omitted thus assumes considerable importance. There is also concern that returning IFs will enhance the likelihood of subjects’ viewing genomic research studies as primarily diagnostic or therapeutic exercises—a type of “therapeutic misconception.”(22)

As part of a set of studies to assist with the articulation of policies governing the return of IFs, we undertook to ascertain researchers' and participants' views. Although ethical policies cannot be based on stakeholder preferences alone, knowledge of those preferences can help to assess the consequences and costs of various approaches.(23) Moreover, policies that differ significantly from the moral intuitions of most researchers may not be implemented effectively. We conducted a large-scale survey and in-depth interviews with samples of genomic investigators, and parallel interviews with a sample of participants in genomic research. Previous papers reported investigators' views on whether they should offer to return IFs to research participants, and if so, which IFs, how those decisions are made, and what the consequences of the process are likely to be. (24,25) A large majority of researchers surveyed thought that participants should be able to decide what types of IFs they receive, from a broad range of options. Here, we report data on investigators' and genomic study participants' views of the informed consent process, and their preferences for how it should be conducted. We draw on these data to provide suggestions for investigators, IRBs, and regulators as they shape the consent process for return of IFs in genomic research.

METHODS

Subjects

We identified genetic researchers for the interviews and survey by: 1) searching the NIH RePORTER database for principal and co-principal investigators of currently funded grants using a combination of key words (e.g., human genetic, human genomics, genetic epidemiology, exome sequencing, whole genome sequencing, genome wide association); and 2) applying similar criteria to abstracts from the 2011 American Society of Human Genetics (ASHG) meeting. Only investigators whose research focus was human disease gene identification were included. Email addresses were identified using online resources. Researchers outside the U.S. and those for whom no email address was found were excluded. Of the 787 researchers invited to participate in the survey, 30 email addresses were incorrect, and 23 researchers indicated that they were not conducting relevant research. 254 of the remaining 734 researchers responded to the survey for a response rate of 34.7%. Responses from 13 individuals were excluded from the analysis because they failed to answer at least 50% of the questions.

Eighty-eight of the researchers who were identified from the 2011 ASHG meeting abstracts were invited to participate in a telephone interview. Purposive sampling was used to insure diversity of geographic location across the U.S., types of institutions (public and private academic medical centers, NIH), types of researchers (physician scientists, basic scientists, statistical geneticists, epidemiologists, biobankers, study coordinators), and disease focus. 25 agreed, were interviewed and were excluded from the invitation for the survey (55 failed to respond, 6 declined, and 2 messages bounced). Survey respondents who indicated that they had returned IFs (n=30) were also asked if they would be interested in participating; 4 agreed and 3 were interviewed. In addition, we identified an opportunity sample of 29 research subjects for interviews, from studies focused on a variety of genetic disorders involving whole exome sequencing at Columbia University Medical Center. Nine declined or did not return phone calls; 20 were interviewed.

Instruments

Relevant portions of the researcher survey were based on a comprehensive review of the literature on informed consent for return of IFs, including multiple-choice questions and free-text responses. It was reviewed by 6 researchers, 2 genetic counselors, and 2 research coordinators, with revision of ambiguous questions. The survey was piloted with 10 researchers and took an average of 20 minutes to complete. The researcher and participant interviews paralleled the survey, and were similar but not identical to each other (with some wording altered to be appropriate to each group), utilizing a semi-structured interview format. Both interviews took approximately one hour to complete. This mixed methods approach uses survey data to characterize the views of a large sample of genomic investigators, and interview data to illustrate the themes underlying their responses and participants' reactions.

Procedures

Researchers who were eligible for the survey were contacted by email to solicit participation. They were invited to click on a link to surveymonkey.com, where the first page included an informed consent disclosure and a statement that proceeding with the survey indicated consent to participate. Email reminders were sent to non-respondents one and two weeks after the initial invitation. Investigators were offered a $25 gift certificate for completion of the survey, conducted from August-September 2012.

Semi-structured interviews with researchers and research participants were conducted by telephone from June-December 2012. Researchers who indicated willingness to be interviewed received an informed consent form; verbal consent was obtained prior to the interview. Research participants were initially contacted by telephone by staff from the sequencing study about their willingness to be interviewed. If they agreed, informed consent was obtained by phone and an interview time arranged. Interviewees' privacy was protected by separating identifying information from responses. Procedures were approved by the IRBs of Columbia University Medical Center and New York State Psychiatric Institute.

Data Analysis

Responses from the survey are provided in aggregate form and characterized with descriptive statistics. Interviews were coded and analyzed using grounded theory (26), with the goal of obtaining a "thick description."(27) Each interview was systematically coded in blocks of text to assign "core" codes or categories, using Atlas.ti7 software, with reconciliation into a single scheme and preparation of a coding manual. Areas of disagreement were resolved by consensus, and principal subcategories identified. Codes and sub-codes were then applied by two coders to all interviews, with differences resolved by joint review and consensus. Quotations from interviews are indicated below by R and from free-text survey responses by RS, each followed by subject number.

RESULTS

Subject Characteristics

For an extensive description of the researchers who participated in the survey and interviews, readers are referred to our prior reports.(24,25) In summary, the researchers who responded to the survey (n=241) were diverse, including PhDs (51.9%), MDs (19.1%), MD/PhDs (13.3%), MSs (7.9%) and others (7.9%). They were predominately male (64.3%) and non-Hispanic white (73%), with a mean age of 43.2 years. The majority had used whole exome (55%) or genome (74%) sequencing in their research, and 48% had obtained consent from research subjects.

Of the researchers interviewed (n=28), 29% were MDs, 50% PhDs, 14% MD/PhDs, and 7% had MS degrees. 61% were male; 68% had performed whole exome or genome sequencing and 11% planned to do so. 54% had generated IFs, 39% had returned IFs, and 39% had returned primary research findings. There were 20 full professors or equivalents, 2 associate professors, 3 assistant professors, and 3 non-academic track titles.

Research participants interviewed (n=20) were mostly female (85%) and non-Hispanic white (85%), with a mean age of 44 years. Twenty percent had high school diplomas, 10% some college, 40% college degrees, and 30% graduate degrees. Eighteen participants were sequenced as part of the assessment of their children's disorders; indications included developmental delay (4), multiple congenital anomalies (2), congenital diaphragmatic hernia (2), and various other congenital syndromes; 2 affected participants had breast cancer and congenital heart disease.

Disclosure of Potential Benefits and Risks

A majority of researchers who responded to our survey endorsed disclosure of each of the possible benefits and risks offered as options (Tables 1 and 2); more than two-thirds agreed with all but two items. Interestingly, although respondents found it difficult to reject disclosure of any particular benefit or risk, in interviews many expressed concern about overwhelming participants with information:

> The problem with the consent process is whether to be as detailed as you want. I'm always very fearful that a subject is just going to turn off and just sign, or just say, "Forget it," because we come up with these well-intentioned, but terribly long consent documents. (R18)

Researchers' perspectives on disclosure of risks and benefits were echoed even more strongly in our interviews of research participants. Almost all genomic study participants endorsed disclosure of each suggested benefit and risk, with no item attracting less than 80% support. However, several participants expressed concerns about being overwhelmed with information:

> P10: Like if you have a five-page consent form, the participant will probably not understand a single paragraph, or they'll not even read a single paragraph in the form. If you make the form shorter, they will probably take a closer look at it, and pay attention to what's in the form.

Disclosure of Information Regarding Impact on Family

Researchers who responded to the survey were strongly supportive of discussing the potential implications of genomic data for family members in the consent process: 92% favored disclosing both "the possible implications of incidental findings for [participants'] relatives" (n=218) and "the potential importance of participants sharing information with them" (n=219), while 79% (n=188) endorsed disclosure of "the possible impact of findings on family relationships." One researcher noted the importance of

> "identification of variant[s] in relatives—they may be in age range or gender where finding is significant; subject may not, but disclosure may still be beneficial. This counts just as much as the subject's results." (RS151)

Genomic study participants also believed that this information should be discussed with them, with endorsement of these items ranging from 65–85% (n=13 to 17). However, our interview data suggested that not all researchers were prepared to have these discussions: "We've not really thought about what results may mean for family members because our researchers have not done family-based recruitment." (R19)

Disclosure of Issues Related to Return of Data from Impaired and Deceased Participants

Although impairment or death of research participants is always a possibility, in studies targeting conditions likely to result in death (e.g., pancreatic cancer) such events are a near certainty. Thus, 64% of researchers surveyed (n=150) thought participants should be told at the time of initial consent how IFs from genomic research with implications for relatives will be handled if they die before the findings are available; and 66% (n=154) felt similarly about discussion of procedures for participants who become incapable of making decisions. Of the research participants interviewed, 90% (n=18) and 95% (n=19) respectively endorsed these items. However, one researcher highlighted the complexities of these discussions:

> I think the issue of what to do if someone dies is an important but difficult question. Since I work with cancer patients, often at the time of diagnosis they are often not ready to talk about what happens if they die, and I could see having this discussion could easily cause them to become angry and not enter the study. (RS1)

A strong majority of both groups believed that in the event of incapacity a legally authorized representative (family member or guardian) should be permitted to decide which, if any, IFs are returned (researchers: 75% (n=177); participants: 95% (n=19)).

Disclosure of Other Information

Researchers surveyed endorsed disclosure of several other categories of information including the possibility of IFs from subsequent studies involving banked samples or archived data (69%, n=164), data security procedures (86%, n=205), and penalties for researchers' failure to protect or properly use information (47.9%, n=114). 76% (n=180) of responding researchers said participants should be allowed to decide whether returned IFs are placed in their medical records. Asked whether there were other categories of information that would be important for participants to know, several survey respondents identified paternity issues, with one specifically including the possibility of incest. Several

interviewed researchers discussed the complexity of adding information about data sharing to the informed consent process:

> It adds another whole layer of the informed consent and counseling process to explain that you're going to put all this stuff on the web, it's going to be de-identified, except there will be enough information there that if somebody knew enough about you they could probably find you and there would be phenotype information linked to it… That would've added another hour. (R23)

Obtaining Consent for Recontact

With ongoing advances in identification of pathogenic variants, sequenced genomes are likely to yield additional IFs in the future. Although there is not yet consensus regarding the extent of the obligation, if any, to re-review previously sequenced data, there was considerable support for obtaining consent for potential recontact in the initial informed consent. 78% (n=188) of researchers endorsed this approach, as did all of the interviewed research participants (n=20). Nonetheless, researchers' practical concerns about recontacting participants were substantial:

> What happens if we find something 10 or 20 years from now? I don't know. We'd definitely contact our clinician, but is our clinician still there? Would we even have contact with the patient anymore? I've never seen that in the protocol. (R25)

Obtaining Assent for Sequencing of Children

When asked whether there was an age above which they would require assent from the child as well as the parents, 52% of researchers surveyed (n=122) said there was. Ages ranged from 7–17 years old, with the vast majority 12 years or older (mean 13.66 +/−2.67 years). Genomic study participants were not asked explicitly about assent, but in response to other queries, a majority indicated that decisions on return of IFs should rest with parents, who would decide whether to communicate the information to their children.

Overriding Participants' Decisions with Regard to Return of Incidental Findings

A narrow majority of survey respondents (56%; n=132) said they would never override a participant's decision to receive or not to receive IFs. However, 33% of investigator respondents (n=78) said they were uncertain, and 12% (n=28) indicated they might override such decisions. The most commonly cited situation when override could occur was when data would have important clinical consequences for the person. Several respondents also said they would return IFs regardless of participants' desires where the well-being of a participant's child might be at stake, "E.g., participant is a middle-aged man with 3 young daughters and he is found to be homozygous for a highly-penetrant BRCA1 mutation." (RS41) If a participant's decision could be overridden, 71% of researchers said that this should be conveyed at the time of consent. Although this question was not posed to the research participants, all of them (n=20) said that participants should be allowed to choose whether results are returned.

Process Issues in Obtaining Informed Consent

Figure 1 displays researchers' views on a reasonable amount of time for informed consent regarding return of IFs. 44% would spend 15 minutes or less, while 77% would not exceed 30 minutes. Genomic study participants' responses ranged from 5–10 minutes to 2 hours, though several replied, "however much time it takes." Several researchers interviewed stressed the importance of interpersonal interactions, not just consent forms. One researcher said about both initial consent and later interactions:

> You have to tune into the person, what their needs are, and their level of understanding. I tend to err on the side of trying to give them a lesson in what the genetics of this are, and walk them through this as systematically and slowly as I can – what we've found, and what it does or doesn't mean – functioning as an educator. It depends a lot on the perception you have of how much the patient is able to understand and wants to understand. We don't handle it exactly the same way every time. (R7)

Indeed, one researcher suggested that genetic counseling take place before participants make decisions about return of incidental data:

> At this point in time, there is so much ambiguity about interpreting genetic data and misunderstanding in the general public about genetic risk that I think incidental findings should only be returned after participants have received genetic counseling, both before consenting and before receiving information. (RS22)

71% (n=169) of researchers surveyed were concerned that obtaining consent for return of IFs might lead participants to confuse a research study with clinical testing (i.e., to manifest "therapeutic misconception"). One researcher worried "that participants may conclude in the future that they have undergone a complete genetic evaluation as opposed to just finding out about unexpected results." (RS53)

DISCUSSION

The challenges in obtaining informed consent for the return of IFs to genomic research participants are evident in our data. Researchers and participants alike embrace disclosure of a wide range of benefits, risks, and ancillary information, including potential impact on family members, protections for confidentiality, and how IFs will be dealt with in the event of death or incapacity. Additional decisions that our researchers endorsed as part of consent included whether IFs should be entered into the medical record, and whether participants desired recontact if future advances identified IFs of medical or personal significance. Given that potential research participants must, at the same time, be told about and decide whether to enter the study for which sequencing is being performed, an enormous amount of information would be in play.

At the same time, in-depth interviews with genomic researchers and research participants revealed that both groups were aware of the risk of subjects being overwhelmed by such comprehensive disclosures and unable to assimilate the information. Indeed, the contrast between the number of IF-related disclosures endorsed by researchers and the amount of time they were willing to spend discussing these issues (nearly half of surveyed researchers

want to spend less than 15 minutes; fewer than 25% would spend more than 30 minutes) was particularly striking. Both groups evidenced a commitment to "full disclosure," which reflects a glaring disjunction with the practical need to keep informed consent procedures comprehensible and brief. Any successful approach to informed consent to the return of IFs must somehow resolve this tension.

At the inception of this study, we envisioned our challenge as identifying the information that should be disclosed to obtain valid consent for return of IFs. However, our results suggest that more than this is needed: standard approaches to obtaining informed consent are not likely to be effective at conveying all the information identified by our respondents as worth communicating. Recognizing this dilemma, some of the researchers we surveyed volunteered possible solutions. One respondent asked, "What about offering to give subject the raw data without interpretation? They could then seek interpretation if they wanted, possibly from a center set up for that purpose, but paid for on a fee-for-service by the participant." (RS118) Some investigators wanted to turn the consent process over to genetic counselors or other staff. A few respondents eschewed consent altogether, suggesting that they would decide which IFs should be returned. However, a more representative comment came from one researcher who noted, "This is important and needs sensible suggestions, not 30 pages of rules. The consents need significant simplification as even the study staff do not understand most and the parents/subjects are usually mystified about the vast majority of the information." (R97)

Reconciling decisional autonomy and the constraints of clinical research is by no means unique to genomics.(28,29) Some commentators have questioned the necessity of research subjects understanding the information they receive (30,31), spurred in part by findings that the length and complexity of consent forms exceed the ability of most participants to comprehend.(20,21) However, those arguments seem less persuasive in the context of genomic research, where participants face choices about receipt of potentially life-altering information. Thus, efforts to promote effective consent seem essential. A much-cited review suggested that interactive discussions with trained personnel are likely to have the greatest positive impact on subjects' understanding (32), but this approach is the most expensive and least likely to be implemented. Assuming that we maintain a commitment to participants making informed choices about receipt of IFs, innovative solutions are needed.

We can envision four models—several of them already being tested—that might be used here: 1) Current informed consent practices would be made more effective and efficient through the development of standardized teaching materials, including videos and interactive computer-based programs, that could be sent to potential research participants in advance, so they can review them repeatedly, if necessary.(33–36) Such an approach would lift much of the burden from the researcher obtaining consent, allowing in-person interactions to focus on reiterating key points and responding to questions. 2) Staged consent would replace current practices. Participants would be alerted at the beginning of a study to the possibility of IFs, with additional information provided, when and if IFs are found, to facilitate an informed choice about whether to receive those data.(37) In an interactive version of the staged consent model, a web-based portal, with links to extensive information about the options, would allow participants to select those results they desire to receive, and

to return at any time to update preferences, receive additional information, and provide follow-up data.(35,36,38,39) 3) Consent to return of specific categories of IFs would be obtained as a condition of enrollment in the study (e.g., as with the ACMG recommendations for clinical sequencing)(40). Although this would not obviate the need for disclosure of information related to IFs, participants would not need to make choices about types of data to be returned. 4) Researchers would not obtain consent regarding IFs, but would provide participants with the raw data, indicating that they are free to pursue interpretation of the findings on their own. This would effectively "outsource" the consent process to third-party providers. We lack the space here to enumerate the comparative advantages and disadvantages of these approaches, but note that they all have positive aspects, though no option is ideal.

The limitations of this study include the uncertain representativeness of our respondents. Our rate of survey responses from genomic researchers (35%) was less than we had hoped for, reflecting the difficulty of engaging busy researchers in survey studies, and the respondents may not fully reflect the opinions of the field. Moreover, some respondents were quite explicit about not having dealt with these issues (only 12.4% had returned genomic IFs), leaving us uncertain whether their responses might change as they gain experience. The interview samples of researchers and research participants were not intended to be representative, and the latter came from a single research center. Hence, additional efforts to survey larger and more representative samples of research participants are needed. Finally, as in all interview-based studies, we cannot rule out some degree of social desirability bias, i.e., respondents telling us what they thought was socially appropriate. However, the diversity of responses we received and the apparent frankness of our subjects suggest that this was not a major concern.

If genomic research continues down the current path of offering to return at least some IFs to participants in sequencing studies, the question of how best to obtain informed consent cannot be ignored. Our data suggest that the major dilemma will be how to support participants' decision making in a manner compatible with the realities of the contemporary research setting. More creative approaches to informing potential participants would appear to be the logical—and necessary—solution.

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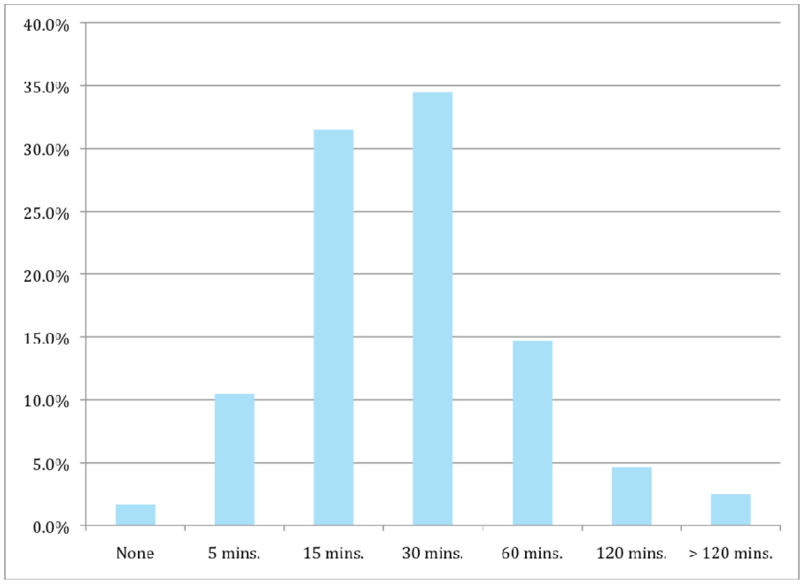

Figure 1.

Researchers' Views on Amount of Time that Should Be Allocated for Informed Consent on Return of IFs (n=238)

Table 1

Views of Researchers and Genomic Study Participants on Benefits of Returning IFs that Should Be Disclosed as Part of Informed Consent[1]

	Researchers (n=241)		Participants (n=20)	
Benefits	**%**	**Count**	**%**	**Count**
A treatable disorder might be identified	94.5	225	95	19
Prophylactic measures may be available to prevent some disorders	84	200	95	19
Modern reproductive techniques (e.g., preimplantation genetic diagnosis) may allow carriers to have children with minimal risk of specific disorder	63.4	151	85	17
Knowing pharmacogenetic status can increase the likelihood of efficacy of some medications and reduce the chance of adverse reactions	67.6	161	90	18
Knowing one's propensity for developing particular conditions can help with life planning[2]	57.6	137		
Knowing whether or not they carry a disease mutation can relieve anxiety for some people[3]			85	17

[1] Researchers' responses derive from an online survey; participants' responses are drawn from a semi-structured interview.

[2] Question asked only of researchers

[3] Question asked only of participants

Table 2

Views of Researchers and Genomic Study Participants on Risks of Returning IFs that Should Be Disclosed as Part of Informed Consent[1]

	Researchers (n=241)		Participants (n=20)	
	%	Count	%	Count
Risks				
The risk of false positive findings[2]	94.5	225		
The risk of false negative findings [2]	85.7	204		
The findings may be wrong[3]			90	18
Possible negative psychological responses	82.8	197	90	18
The danger of falsely concluding from a negative result that they are not susceptible to a disorder, e.g., because of limitations of the testing and existing knowledge	78.6	187	90	18
Possible confusion resulting from the ambiguity of the results	76.1	181	80	16
The possibility that the interpretation of the findings might be different in the future as more knowledge is acquired	85.7	204	90	18
The risk of stigma/discrimination (e.g., in insurance) if information about their test results becomes known	71.8	171	90	18
Possible need for further testing, counseling and follow-up, and the unavailability of funds from the study to pay for it	84.9	202	85	17
Risks to data security and confidentiality	53.4	127	85	17

[1] Researchers' responses derive from an online survey; participants' responses are drawn from a semi-structured interview.

[2] Questions asked only of researchers.

[3] Question asked only of participants.