Genetics Researchers' Perceived Obligations to Return Incidental Findings and Individual Research Results to Participants

by
Caroline Evans Young

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ABSTRACT

Background: Clinical investigators are increasingly facing decisions about returning individual research results (IRRs) and incidental findings (IFs) from genome sequencing to research participants. Studies have shown that participants are interested in receiving results. Yet there has been debate in the bioethics community about the extent of researcher obligation to return both IRRs and IFs. Little research has focused on whether researchers perceive that they have an ethical obligation to return results, and whether such perceptions predict the return of results**.**

Objective: This study examines researchers' perceptions about and predictors of their obligation to return results to participants. Further, we report on whether perceptions of obligations are concordant with reported practice.

Methods: Human genetics researchers identified through the American Society of Human Genetics (ASHG) and the National Institutes of Health database of genotypes and phenotypes (dbGaP) were invited to complete an online survey conducted by the Genetics and Public Policy Center seeking to describe perspectives about current issues in genetics including consent, privacy protections, data sharing, and the return of individual research results. This study, a secondary data analysis, seeks to describe the extent of researchers' perceptions of legal and ethical obligation to return results, describe predictors of such attitudes, and describe factors related to the reported return of results to participants.

Results: Genetics researchers varied in the extent of their perceived obligation to return IRRs and IFs to their participants. While the majority of researchers (68%, n=242) support returning IRRs or IFs to participants, less than half reported feeling an obligation

to return results (IRRs: 44%, n=158; IFs: 44%, n=157). Multiple linear regression showed that the use of clinical samples was predictive of higher perceived obligation to return results ($p<0.01$), while work setting was also predictive of feelings of obligation ($p<0.05$). The majority of genetics researchers (60%) do not return any IRRs or IFs to their participants. Further multivariate analysis revealed that those with higher perceived obligation and those with more interaction with participants were more likely to return results ($p<0.01$). Among those who do not return results, there were many influences on their decisions including lack of useful results generated as well as barriers associated with IRBs, consent constraints, and level of contact with participants.

Conclusions: These results provide insights into how researchers are thinking about their ethical obligation to their participants, and suggest that the extent of this obligation and the level of interaction with participants are associated with the return of IRRs and IFs. In the current research climate with a paucity of overarching guidelines on the topic, research teams often determine actual practice. This research suggests that these decisions are informed in part by the amount of interaction researchers have with their participants and the amount of perceived obligation felt by researchers, which provides assistance in thinking about how future guidelines may be conceptualized.

Thesis Readers
Barbara B. Biesecker, PhD, MS (Advisor)
Lori Erby, PhD, ScM

Thesis Committee
Barbara B. Biesecker, PhD, MS (Advisor)
David Kaufman, PhD
Lori Erby, PhD, ScM

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INTRODUCTION

With the growth of genome sequencing studies in recent years has come debate about whether researchers have a duty to return individual research results (IRRs) and incidental findings (IFs) to research participants. IRRs are results that reflect the intended study goals, such as identification of gene variants that caused a condition under study. An IF is defined as "a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study," (Wolf *et al*., 2008). Studies have shown that, along with altruistic intentions to contribute to research, one of the main motivations of participants joining genome sequencing studies is to learn more about genetic factors that affect their own health risks (Facio *et al*., 2011). Quantitative findings suggest participants have interest in return of all types of results, although interest is greatest in medically actionable and carrier results (Facio *et al*., 2013). Focus groups of participants of ClinSeq®, a National Institutes of Health Intramural cohort study investigating the use of whole genome sequencing as a tool for clinical research, examined preferences for delivery of IRRs. These data demonstrate a strong preference to learn nearly all types of results, with the exception of risks results related to some neurologic conditions. However, the ease with which participants seemed to change their views suggests that they are newly formed and subject to change (Wright *et al*., 2014). Other studies have also shown that participants would like to receive IRRs in exchange for participating in research, and that they believe researchers have an obligation to share results with them (Bollinger *et al*., 2012). Migrating preferences, meaning those that change over time, have been reported with the roll out of other new technologies (Fischoff 2013) suggesting the importance of exploring underlying values relating to decisions to use new

technologies. Although preferences of research participants have been reported, the perspectives of researchers on the decision whether to return is less well characterized.

Several guidelines have been published on return of research results and incidental findings in genetic studies. Most stakeholders agree about the broad categories of results that should be offered to research participants, if not about the logistics of how to do so (Brandt *et al.*, 2013, Fabsitz *et al.*, 2010, NBAC 1999). Most of these guidelines do not distinguish between IRRs and IFs (Haga and Zhao 2013). In the realm of clinical sequencing, the American College of Medical Genetics and Genomics released a recommendation for clinical diagnostic laboratories to return medically actionable secondary findings to all patients regardless of patient preference (Green *et al.*, 2013). This recommendation was later updated to include an option for patients to opt out of receiving these results. However, controversy still exists around these and other guidelines and the extent to which they should be followed in research settings, and actual practices vary. In the research setting, similar conclusions were reached by the National Heart, Lung, and Blood Institute Working Group on Reporting Genetic Results in Research Studies, which released recommendations about the return of genetic results from research studies (Bookman *et al.,* 2006). They stated that genetic results should be returned to participants when the associated risk for the disease is significant, the disease itself is associated with significant morbidity, and there are interventions available to mitigate the course of the disease. These guidelines imply the existence of an obligation of researchers to return research results that meet these criteria.

The guidelines that are in place to suggest ethical practices are not recent or always specific to research results. Often the distinction between guidelines for clinical care and

research are indistinct. Some may be created by professional societies, such as ACMG, and imposed by IRBs of research institutions. Often researchers are left to decide the extent particular guidelines pertain to their research practices. Important questions include whether guidelines are being followed, and whether researchers think they are reasonable. One study conducted by Heaney and colleagues (2010) used an online survey of authors of genetic and genomic research publications between 2006 and 2007 to investigate researcher practices on returning genetic research results. More than half (54%) of respondents had considered the issue, 28% offered to return IRRs, and 24% actually provided results. Researchers with a medical degree were significantly more likely to offer to return results than those with PhDs (OR 2.8). Only a small number of those who indicated that cost and time were barriers to returning results during the planning stages of their study also said that these factors ultimately influenced their decision. Instead, the more frequently cited reasons were concerns about clinical validity and respect for their participants. This study's limitations include the small sample size (105 participants from response rate of 24%) and a possible response bias reflecting those familiar with the issue (Heaney *et al.*, 2010).

Bioethics Perspective

Many bioethicists have weighed in on the relationship between researchers and participants in genomics research, laying out potential frameworks for considering informed consent and the responsibilities and rights of each party (Beskow 2007; Meyer 2008; Wolf *et al.,* 2008; Beskow and Burke 2010). The broader discussion about return of research results in general (not just in genetics) generally supports the return of results

from research. A 2000 Summit Series on Clinical Trials in cancer concluded that returning results should be the "ethical norm" even if the information would not necessarily improve the participant's health. Beyond health benefits, returning results from research may empower participants to be proactive in other general areas of their health and take an interest in the process of research, strengthening the relationship between researcher and participant. Based on the evidence that participants are eager to learn what they can about their genes from researchers, some ethicists view researchers as having a duty to return results based on respect for participants and their preferences. In contrast is the view that it would be too much of a burden to require researchers and biobank managers to routinely return results to all participants and contributors (Ossorio 2012). These contrasting perspectives could result in stalling the overall scientific endeavor. In returning genetic research results to some people now, researchers may be failing to help a greater number of people because of delayed research and missed discoveries. Additionally, depending on the research, the quality and utility of the results being returned may be of questionable or no value. Another argument against the return of results that researchers have cited is the lack of clinical expertise for results delivery.

As such, some bioethicists have framed the discussion as a conflict between collective responsibility/societal good and autonomy/individual rights. Most advocate an approach somewhere in between requiring return of all results and forbidding that any be returned. The determinants of where an individual researcher's practice falls on this continuum would be decided by: the context of the study, the analytic validity and clinical utility of a particular test, and the potential personal meaning of a result (Ravitsky and Wilfond, 2006). There is agreement among bioethicists that it is important to

distinguish a research result from a clinical finding, and that recommendations in these two settings should correspondingly differ. For example, one ethical framework upholds that the threshold for returning results based on the clinical utility of a result from a research study should be lower than the clinical use of the same result, meaning that the same result may be associated with an obligation to return for clinicians, but not for researchers (Ravitsky and Wilfond, 2006). Further, the context of the research should be considered, as well as the length of time the study continues, with a greater obligation to return results in instances in which research participants are involved with a study for a longer period of time. Over time, more will be learned in genetics, complicating discussions about how long researchers are obligated to update participants on the interpretation of results (Manolio 2006).

Legal Obligation

In discussing the return of research results and incidental findings, there are two kinds of obligation that can be considered. Ethical obligations, as described above, result from moral considerations. Legal obligations, on the other hand, come from liability concerns. In a 2014 review of US and international court cases, McGuire and colleagues examined the liability risk and disclosure of clinically significant research findings (McGuire *et al.*, 2014). Within the research setting they considered cases related to both clinically significant research results and incidental findings. At the international level, there has been a strong trend toward an emerging legal duty to return results (McGuire *et al.*, 2014). The European Convention on Human Rights and Biomedicine (Oveido Convention) and multiple national laws have shown a legal obligation to disclose

clinically significant research results to participants and their families. In the United States, on the other hand, legal obligations are less clear (McGuire *et al.*, 2014). The potential for liability from failing to return a genetic incidental finding is as yet unknown (Pike *et al.*, 2014). There is no clear line between research and clinical care that determines a researcher's duty, muddying the waters both ethically and legally, since it is not clear where tort liability could apply.

The Common Rule (45 Code Fed. Reg. Part 46), a US federal regulation that focuses on human subjects research, does not explicitly require the return of results to research participants. The Office of Human Research Protections (OHRP) has similarly not spoken to the return of results, leaving it largely up to individual Institutional Review Boards (IRBs) to address the issue (McGuire *et al.*, 2014). No court case in the US has directly addressed whether there is a legal duty for researchers to disclose significant findings to individual participants. Without precedent or clear legal guidelines for behavior, determination of whether to return results is left to the researcher. McGuire and colleagues suggest that as more court cases arise, legal obligations will begin to depend on "the type of research being done, the ways in which the research data are collected and stored, and the researcher's relationship with the study participant, as well as emerging consensus on appropriate professional behavior" (McGuire *et al.*, 2014, p. 10).

Overall, in the absence of clear legal statements regarding obligations about the return of individual research results and incidental findings in the United States, the decision falls to individual IRBs and researchers. Similarly to McGuire and colleagues, Pike and colleagues described the current state of legal obligations by genetics researchers to return incidental findings to participants (2014), arguing that it is generally

unclear where liability could arise. Because there is not yet a clear-cut policy or a history of case law on the topic, the current potential to be held liable depends on ethically related concerns such as guidance documents and customary practice, factors in which there is no consensus. Fear of liability, McGuire and colleagues argue, may drive behaviors (2014). Determining whether researchers believe that returning results and incidental findings could expose researchers to legal liability is an important step towards determining their perceptions of legal obligation.

Ethical Obligation

Deontology is a theory that has been used to describe the resolution of ethical tensions in corporate realms. The name of the theory comes from the Greek work *deon*, which means duty or obligation. Overall, the theory centers on people's perceptions of their obligations and how these perceptions shape later behaviors. One of the theory's constructs is "bounded autonomy," which refers to "perceptions, namely an understanding or interpretation of the extent to which free behavior is circumscribed by moral norms" (Folger *et al.*, 2013). To the extent that people have a say in the amount and type of behaviors that are undertaken, deontologic theory posits that more significant feelings of obligation will lead to more engagement. People who feel obligation about an outcome will be more likely to see behaviors that lead to those outcomes as justified and thus will be more inclined to engage in these behaviors (Folger 2012). In research ethics, deontology is a common school of thought used to deliberate bioethical dilemmas. Applying this framework to the return of genetic research results, the extent to which researchers choose to implement guidelines and decide which results to return would

depend in part on how much obligation they feel to their participants and whether they have ethics approval to return results.

As described above, in the absence of clear legal requirements, it is left up to researchers and IRBs whether to return genetic IRRs and IFs. A 2012 in-depth interview study with 31 IRB members throughout the United States focused on IRB perspectives on this issue (Dressler *et al.*). The investigators found that many of the people that they interviewed were not comfortable with their expertise in genetics, and most had not faced the issue in the course of their work with the IRB. There was also disagreement among them about the role of the IRB in this instance. While some felt that the IRB should have active involvement in the issue of return of results, others thought that they should merely have an oversight role, such as helping to frame the ethical considerations for the researchers, leaving the decision to them. Neither the amount of time on the IRB nor experience with assessing risks of genetic research seemed to influence participants' view of the IRB's role (Dressler *et al.*, 2012). Clearly, there is no consensus on how best to make the decision about the return of genetic IRRs and IFs, either legally, or by IRBs. Interviews with IRB members suggest that researchers typically have some say in the process, either by making the decision themselves (with IRB guidance) or by partnering with IRBs to help members understand the issue, which could influence how the institution addresses return of results in the future. Even in the presence of multiple guidelines by organizations in the US and abroad (Council for International Organizations of Medical Sciences 2002, Fabsitz *et al.* 2010, and UNESCO 2003), previous research shows that genome researchers are not regularly returning IRRs and IFs to participants (Heaney *et al.*, 2010, Fullerton *et al.*, 2012, Ramoni *et al.*, 2013). Thus,

ascertaining researchers' perceptions of obligation to return results is a crucial step in understanding practice variation. If there is a discrepancy between attitudes and reported behavior of return of results, perhaps new practice guidelines need to be constructed.

Little research has been done to examine whether researchers, as bioethical theorists describe, feel an obligation to return research results and incidental findings. This study examines this question, as well as the relationship between researchers' perceived obligation and their behavior returning such findings to participants. Only one previous paper has examined this question in depth (Fernandez *et al.*, 2013), and this was done in a Canadian population of pediatric genetics researchers (mostly in rare diseases and cancer). Thus, generalizability to a broader range of human geneticists in the US population may be limited. However, the study found that age, years in practice, country of training, and comfort with discussing genetic results were all unrelated to attitudes about obligation. They did find that medical geneticists were more likely to report feeling greater responsibility to examine their participants' data for IFs than genome researchers. The authors did not have adequate data to determine whether MD versus non-MD status explained this difference. Based on these results, the related finding by Heaney and colleagues (2010), and the expectation that clinicians will feel a greater ethical obligation to return results to their participants/patients than those who identify primarily as basic scientists, we hypothesized that, in this study, researchers who identify their research area as clinical genetics would have higher perceived ethical obligations to return results (both IRRs and IFs) than those in the other categories.

As described above, there are two main types of obligation at play. This study examines perceived ethical obligation to return IFs and IRRs as well as perceived legal

obligation. It also describes demographic variables that may be associated with obligation such as sex, age, and socioeconomic status, educational and work background. Characteristics of the research itself, such as the nature and extent of interaction with participants, as well as the source of the research sample were predicted to be likely to have more of an effect on perceived ethical obligation. Research characteristics included funding source, type of research (clinical genetic, basic human genetic, or bioinformatics), and source of samples (collected by oneself or another group of researchers). Environmental constraints included constraints of consent or IRB, ability to recontact participants, lack of resources, and the existence of an additional ethics committee, advisory board, or review board outside of the IRB.

Although prior studies have also examined the role of research demographic characteristics, characteristics of the specific research study itself were likely to have a greater effect on researchers' perceived ethical obligation than demographic variables. Perceived role plays a large part in one's perception of extent of professional duty (Hardimon 1994). With this in mind, designating that one is a clinical researcher (or working with a clinical population) is indicative of a different sort of relationship with participants than a researcher working with samples they did not collect from a clinical population. It was hypothesized that level of connection with participants, as shown through the amount of time they spend with participants (more time associated with higher perceived ethical obligation) and the type of population that the samples come from, will be associated with more perceived obligations to return results. Overall, this gets back to the researcher's role (or perceived role). Those who spend more time with their participants and who view their participants as clinical "participant patient" were

predicted to be more likely to translate that relationship to one that requires a perceived obligation to return IRRs and IFs.

Yet, as Clayton and Kelly point out, there is sometimes a gap between what people would like to do and their ultimate actions (2013). Ramoni and colleagues found that although 69% of the investigators they studied believed that returning genetic results was warranted in at least some circumstances, only 4% had actually done so (2013). Thus, there are still questions to be answered about the circumstances and contexts of return of IRRs, and how provider decisions are made. Genome sequencing and the ability to interpret the results is still relatively new, and familiarity with genomics may play a role in the extent to which investigators feel prepared to return results. Klitzman and colleagues conducted a qualitative interview study with researchers about their decision-making process for returning incidental findings (2013). They found that information about the variant, participant well-being, perceived responsibility, and input from external factors such as *ad hoc* committees, IRBs, or other policies all factored into their views. Other potential influencers include financial resources and availability of expertise in returning genetic results. Researchers varied in their opinions on who should decide (IRBs, PIs, or participants), and on the amount of guidance they desired from outside entities. The NHLBI Working Group on returning results in genetic research suggested that the decision to return results should not be solely that of the researcher, but instead should be made in conjunction with an IRB of multiple perspectives (Bookman *et al.*, 2006). The burden of responsibility is less clear. Quantitative research can elucidate generalizable findings about who researchers think should be making decisions about the return of results, who is actually making the decisions, and what factors are driving them.

The purpose of this study is to describe researchers' perceptions of legal and ethical obligation to return results to participants, and correlates of ethical obligation, to determine whether obligation translates into reported return of results, and to characterize mitigating factors between stated attitudes and actions. Outcome data may help to inform future policy and guideline revisions related to returning IRRs and IFs in genomic research and to identify potential directions for intervention for those with a goal of influencing researcher behavior or creating consistent practices.

METHODS

Study Design and Participants

This study involved administration of an online survey to gather quantitative data using a cross-sectional design. The topics assessed were part of a larger survey conducted by the Genetics and Public Policy Center (GPPC) that was fielded by the firm GfK (formerly Knowledge Networks).

This one time self-administered survey had 94 items (though some were directed either to biobank leaders or to researchers, but not both), and pilot testing showed that it took 20-30 minutes to complete. The parent survey was composed of demographic questions, as well as practice and opinion questions about consent, privacy, confidentiality, data sharing, and return of results. Survey items were derived from 59 qualitative interviews with researchers conducted by GPPC. The overall purpose of the parent study was to measure researchers' practices, preferences and beliefs about how best to address the practical and ethical challenges presented by human subjects research in biobanking and large-cohort genetic research settings. The parent study systematically assessed: (1) researchers' and biobankers' attitudes, preferences, and reported practices with respect to human subjects issues in genomic research; (2) whether and how these outlooks, preferences, and practices align or conflict with public attitudes and current research guidelines; and (3) what the unresolved concerns of the research community are around these issues. The current sub-study analyzed researchers' data from the demographic and return of results sections, which cover practices and beliefs/opinions about researcher obligation. The specific constructs included demographic variables, research characteristics, attitudes about obligation to return results, actual practices

around returning results, and external factors that might influence attitudes and practices (See questions included in Appendix 1).

The parent study received IRB approval from the Johns Hopkins Medicine Institutional Review Board (study number CIR00001252). The National Human Genome Research Institute (NHGRI) IRB determined that the secondary data analysis was exempt from IRB review per 45 CFR 46 (OSHRP #12333). The survey was anonymous, and participants were able to withdraw at any point while taking the survey.

Email invitations to participate in the parent survey were sent to 3,147 professionals including 1,658 members of the American Society of Human Genetics, 1,262 researchers identified from the public National Institutes of Health database of genotypes and phenotypes (dbGaP), and 227 senior biobank staff on the dbGaP contributor list. Participants were researchers from the United States who were able to take the survey in English. Undergraduate students, graduate students, and post-doctoral researchers were excluded. Researchers' main area of work had to be human genetic or genomic research that was not primarily related to ethical, legal, social or policy issues. Their samples did not need to be collected directly from living participants. Data were collected over eight weeks. For the secondary analysis reported here, only responses from those who identified themselves as primarily human genetics researchers were included.

All survey respondents were offered an incentive in the form of a $10 Amazon gift certificate or a $10 donation to either the ASHG Development Fund (which pays for scholarships and trainee travel to ASHG meetings) or the ISBER travel scholarship fund, based on participant preference. In addition, all participants were entered in a raffle to

win one of five Amazon Kindles. The Genetics and Public Policy Center provided all compensation.

Analysis

Data were analyzed using SPSS version 20. Descriptive statistics were used to present the extent of perceived ethical obligation to return genetic research results to participants. An exploratory factor analysis was conducted on items related to ethical obligation to assess whether the items contributed to a singular assessment of obligation. The factor analysis used Varimax with orthogonal rotation. A single obligation score was then calculated for each respondent by summing the items in the factor. The actual return of results behavior was calculated through a summation of one categorical item focused on reported return of incidental findings ("Do you return IRRs to participants?") and one categorical item focused on individual research results ("Do you return IFs to participants?"). Possible scores ranged from 2-6, with higher scores indicating more active return of results. Multiple linear regressions were conducted to test hypotheses about factors related to ethical obligation to return results and reported practice of return of results. Variables that showed a statistically significant correlation with the dependent variable of interest (ethical obligation and reported practice) were added to the regression and nonsignificant independent variables were then successively removed from the model.

RESULTS

Recruitment and Response Rate

During the recruitment period that ran from March 7-April 7 2014, 3,147 individuals identified through ASHG and dbGaP were sent email invitations to participate in the online survey. A total of 609 individuals responded to the invitation, 548 of which were willing to take the survey. Of the 61 individuals who did not indicate that they were willing to take the survey, 27 said that they were unwilling and 34 did not indicate if they were willing and did not proceed. Of the 548 researchers who were willing to complete the survey 455 (or 83% of willing respondents) were eligible, and 358 of these completed the survey in its entirety for a 79% completion rate among those who were eligible.

The overall response rate was 18% (548/3147). The majority of respondents were recruited through dbGaP. 1,262 dbGaP users were emailed, and 314 responded to the invitation. Forty-six emails were returned with error messages. Of these 314, 280 individuals were willing to participate (22%) and 170 completed the survey. In addition, 227 dbGaP contributors were invited to participate, and 38 indicated willingness to participate (17%). 1,803 individuals were identified through ASHG as potentially eligible to participate in the study. Of these, 145 were ruled out because of pilot study involvement, overlap with the dbGaP contributor list, or not meeting inclusion criteria. The remaining 1,658 ASHG members were sent invitations to participate. Of these, 230 willing to participate, 201 were eligible, and 159 completed the survey in its entirety (9.6%). Overall, 55.6% of those who completed the survey were recruited through dbGaP and 44.4% were recruited through ASHG.

Study Population

The median age of genetics researchers was between 41-50 years old. The majority was male (62%). Primary work setting varied, but the majority of respondents (62%) indicated that they work predominantly in a university/academic setting. The most common primary funding source reported was the National Institutes of Health (66.2%), followed by the researchers' own parent organization (10.6%) and private foundations (7.5%). Table 1 summarizes the characteristics of the sample.

Table 1. Demographics of Researcher Respondents to the GPPC Parent Survey

N=358	n(%)
What is your gender?	
Male	220(62%)
Female	131(37%)
What is your age?	
18-30	5(1%)
31-40	82(23%)
41-50	114(32%)
51-60	97(27%)
61-70	40(11%)
71-80	12(3%)
81+	3(1%)
What is your primary work setting?	
University/Academic	222(62%)
University/Clinical	33(9%)
Other hospital/Health care organization	23(6%)
Other non-profit	2(1%)
Government	18(5%)
For-profit industry	24(7%)
Research Institute	31(9%)
Other	2(1%)
Does your main area of research focus on?	
A particular disease or group of diseases	192(54%)
A broad range of diseases or phenotypes	124(35%)
My research is not disease-focused	33(9%)
Refused	2(1%)
Do any of your samples come from clinical populations	
Yes	368(86.8%)
No	56(13.2%)

Ethical Obligations to Return Results

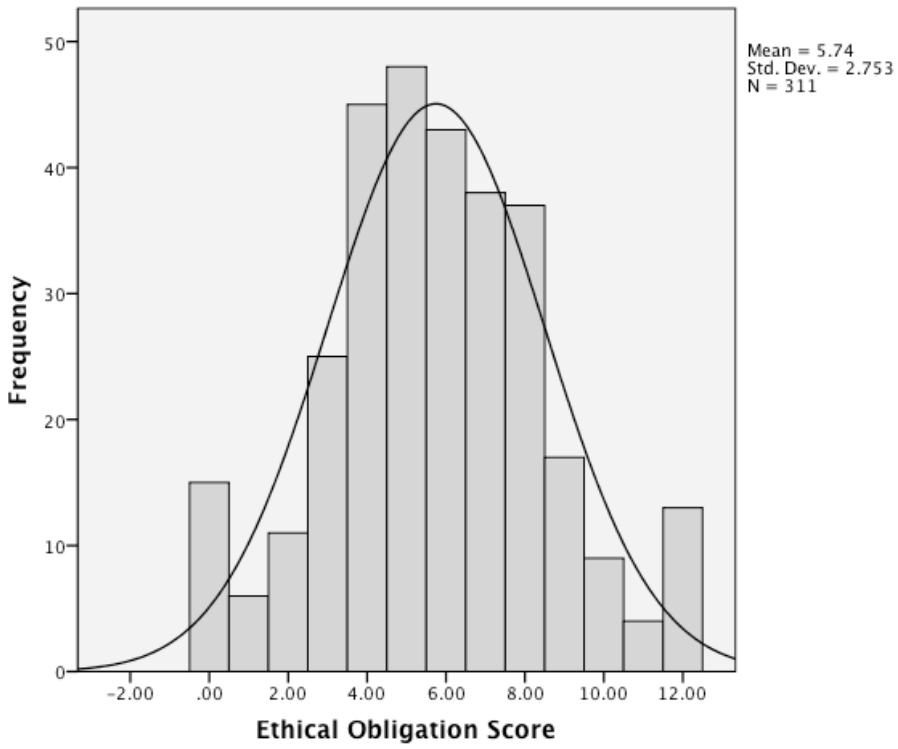
An exploratory factor analysis was conducted in order to determine whether multiple items on the survey assessing ethical obligation were describing the same underlying concept (Table 2). The items, described in Table 2, were each rated on a 4-point modified Likert scale (*0=strongly agree, 1=agree, 2=disagree, 3=strongly disagree*). Based on the factor analysis showing one underlying concept, a single score was calculated for each researcher based on four items representing a single factor (Kaiser-Meyer-Olkin measure of sampling adequacy=0.745). Higher scores on the obligation scale indicate greater perceived obligation to return IRRs and IFs to participants. Scores ranged from 0 to 12, and the mean was 5.74 $\pm$ 2.75 (Table 3). Distribution of scores was approximately normal (Figure 1).

When considering the items independently, though the majority of genetics researchers support returning IRRs or IFs to participants (68%, n=242), less than half report feeling an obligation to return results (IRRs: 44%, n=158; IFs: 44%, n=157). Most researchers (78%, n=279) reported that they had no obligation to look for medically significant variants unrelated to the topic of their research. Researchers were also asked about the legal ramifications of returning results to their participants. 70% agreed that returning IRRs or IFs could expose researchers and biobankers to legal liability.

Table 2. Factor Loadings and Communalities for Four Items Related to Ethical Obligation to Return Research Results to Participants

Variable	Component	% Variance Explained
I do not support returning individual genetic research results or incidental findings to participants	0.730	63.77
I have no obligation to return individual research results	0.896	18.68
I have no obligation to return incidental findings	0.878	11.48
I have no obligation to look for medically significant variants unrelated to the topics of research	0.667	6.07

Figure 1. Histogram of Ethical Obligation Scores



The items concerning ethical obligation were similar in their direct approach to a previous study that aimed to capture obligation as a construct (Fernandez *et al.*, 2013). For example, both surveys asked about examining the data set to look for medically significant findings, and both asked whether genetic researchers have a responsibility to return incidental findings. This, and pilot testing performed by GPPC with genetics researchers indicate acceptable face validity of the ethical obligation measure. The measure was consistent with reported behavior of return of results (a practice that it should theoretically be related to) with a correlation of 0.424, showing additional convergent validity of the factor. Reliability of the ethical obligation measure was shown through a Cronbach α of 0.805, indicating relatively high internal consistency.

Table 3. Descriptive Statistics of Ethical Obligation to Return Research Results

	Ethical Obligation
N	311
Mean	5.74
S.E.	0.16
Minimum	0.00
Maximum	12.00
Range	0.00-12.00
Skewness	0.11
Skewness S.E.	0.14

Table 4. Correlation Matrix for Ethical Obligation to Return Results

	Ethical Obligation	Legal Obligation	Clinical Genetic Research Conducted	Clinical Data Sample Use	Nature of Interaction with Participants	Research Institute Work Setting	University/ Academic Work Setting
Ethical Obligation	1.00	0.298**	0.127*	-0.165**	0.055	0.189**	-0.177**
Legal Obligation	-	1.00	0.067	0.030	0.028	0.065	-0.026
Clinical Genetic Research Conducted	-	-	1.00	-.199**	.332**	0.011	-0.195**
Clinical Data Sample Use	-	-	-	1.00	-0.027	-0.012	0.088
Nature of Interaction with Participants	-	-	-	-	1.00	0.020	0.021
Research Institute Work Setting	-	-	-	-	-	1.00	-0.393**
University/ Academic Work Setting	-	-	-	-	-	-	1.00

* p <0 .05; ** p < 0.01

Table 5. Correlation Matrix for Reported Return of Results

	Reported Practice of Return of Results	Ethical Obligation	Legal Obligation	Clinical Genetic Research Conducted	Clinical Data Sample Use	Samples Collected Directly from Participants	Nature of Interaction with Participants	Ever Served on IRB
Reported Practice of Return of Results	1.00	0.424**	0.124*	0.219**	-0.119*	-0.171*	0.266**	-.107*
Ethical Obligation	-	1.00	0.298**	0.127*	-0.165**	-0.053	0.055	-0.054
Legal Obligation	-	-	1.00	0.067	0.030	0.028	0.028	-0.110
Clinical Genetic Research Conducted	-	-	-	1.00	-.199**	-0.280**	.332**	-0.029
Clinical Data Sample Use	-	-	-	-	1.00	0.104	-0.027	-0.063
Samples Collected Directly from Participants	-	-	-	-	-	1.00	-0.520**	0.095
Nature of Interaction with Participants	-	-	-	-	-	-	1.00	-0.069
Ever Served on IRB	-	-	-	-	-	-	-	1.00

* p <0 .05; ** p < 0.01

Bivariate analyses were conducted to determine which demographic and research characteristics may be correlated with feelings of obligation to return results (Table 5). All variables that were found to be significant at the $p<0.05$ level in the bivariate analyses were put into a multivariate linear regression model with obligation score as the dependent variable in order to determine the significance of the relationships. Consistent with our hypothesis, those who reported that some of their data came from clinical populations felt a higher obligation to return results than those who did not ($p=0.005$, Table 6). Researchers who indicated that their primary work setting was a research institute also reported higher obligation ($p=0.014$). Conversely, a university/academic setting was associated with a lower perceived obligation, though this relationship was not

statistically significant. The combined model explained 6.3% of the variability in ethical obligation score.

Table 6. Multiple Linear Regression for Factors Related to Perceived Ethical Obligation to Return Genetic Research Results to Participants

Variable	B	SE B	β
Constant	7.395	0.555	
Clinical Data Sample Use	-1.255	0.445	-0.156**
Primary Work Setting University/Academic	-0.579	0.341	-0.102
Primary Work Setting Research Institute	1.432	0.577	0.149*
Adjusted R^2	0.063		
F	7.942**		

* $p < 0.05$; ** $p < 0.01$

Return of Results

The majority of genetics researchers are returning neither IRRs nor IFs. Sixty percent of researchers report not returning any IRRs to participants, while 16% "may return a research result if it is deemed important" and 14% have a protocol that includes the return of least one IRR. One in ten said their protocol does not specify an approach to IRRs. Similarly, 60% report not returning any IFs to participants, while 20% "may return an incidental finding if it is deemed important," 4% return one or more IFs, and 15% do not specify an approach.

Further bivariate analyses were conducted to determine which demographic and research variables may be correlated with reported return of results (Table 6). All variables that were found to be significant at the $p<0.05$ level in the bivariate analyses were put into a multivariate regression model with return of results as the dependent variable in order to determine the amount of variance in return of results explained by these variables. Ethical obligation score ($p<0.001$) and nature of interaction with research

participants (P<0.001) were significantly related to reported return of research results (Table 7). Researchers who indicated more ability and practice interacting with participants were more likely to return results to those participants. Similarly, researchers who scored higher on the obligation scale (corresponding to higher perceived obligation to return) reported more practice of returning results. The combined model explained 23.5% of the variability in reported return of results.

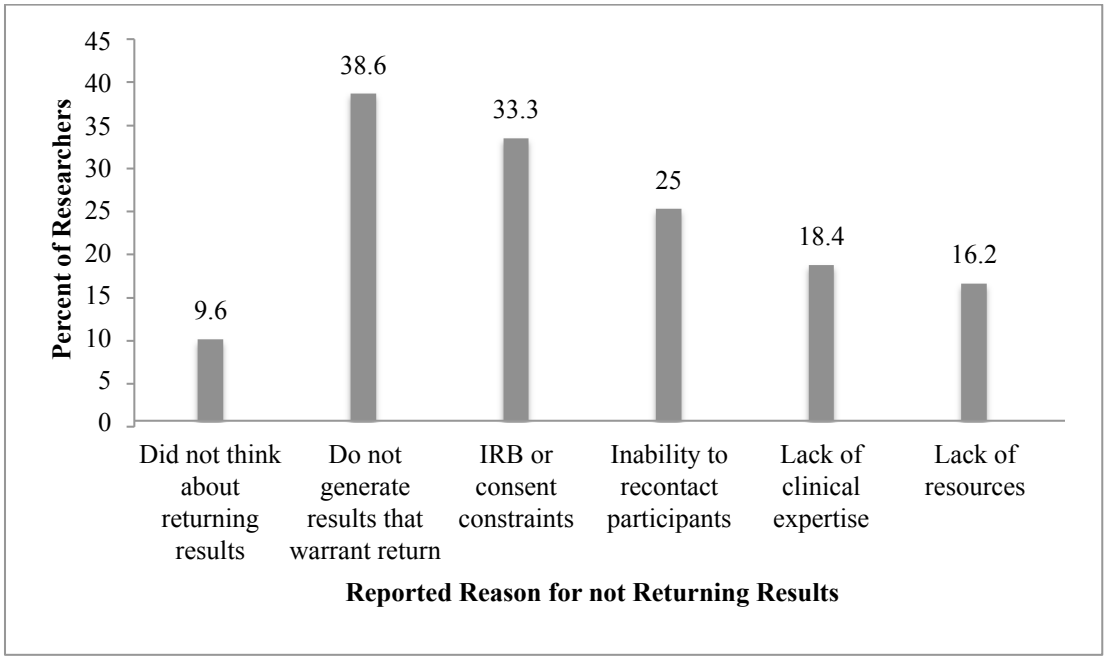
Table 7. Multiple Linear Regression for Factors Related to Reported Return of Genetic Research Results to Participants

Variable	B	SE B	β
Constant	1.397	0.178	
Ethical Obligation	0.178	0.022	0.414**
Nature of Interaction with Participants	0.256	0.053	0.242**
Adjusted R^2	0.235		
F	47.868**		

* p < 0.05; ** p < 0.01

Of the 228 researchers who reported that they do not return genetic results to participants, the most common reported reason for not returning was not generating results that warrant return (38.6%) (Figure 2). Researchers also indicated that IRB and consent constraints (33.3%) and inability to re-contact (25%) influenced their decision. In the free text option for this question, 55 researchers identified further reasons for not returning results. Twenty of these researchers (8.8% of those who do not return results) noted that lack of CLIA certification of their lab was a reason they do not return results. The other most commonly reported reason was the lack of clinical utility of results (n=4 researchers). Figure 2 graphs the influences on researchers' decisions to not return IRRs and IFs. When asked about guidelines for the return of research results, 75% of respondents agreed or strongly agreed that they were unclear or inconsistent.

Figure 2. Influences on the Decision not to Return IRRs or IFs to Participants.



*Percentages do not equal 100%, as participants were allowed to choose more than one response

DISCUSSION

Ethical Obligation

While most respondents supported returning genetic results to their participants, they were divided on their own obligation to do so. A small study of Canadian pediatricians found that few researchers reported a strong obligation to return genetic research results (37%), which was similar to self-reported perceptions of their obligation in the study (Fernandez *et al*., 2013). In the current study, perceived obligation was associated with research characteristics including the use of clinical samples and work setting, as hypothesized. It was similarly correlated with the conduct of clinical research. Interestingly, the extent of interaction with participants was not significantly associated with perceived obligation, though it was related to reported return of results. Consistent with Hardimon's description of perceived role (1994), researchers who work with clinical samples or who self-report that their main research area is clinical likely perceive their role to share clinical characteristics, creating perceptions of an obligation to their participants. Our findings are consistent with Fernandez and colleagues' findings that medical geneticists were more likely than genomics researchers to report feeling an obligation to return genetics IFs to their participants (2013). Similarly, MD researchers have been found to be more likely to return results than non-MD researchers (Healey *et al*., 2010). Similar to the Canadian study, there was no relationship between other demographic characteristics of the researchers and the perceived obligation to return results. Characteristics of the research itself appear to be more important in affecting perceived ethical obligation to return results to participants.

Return of Results

In this study, a minority (30%) of researchers reported that they actively do return IRRs or IFs or may return a research result if it is deemed important. This was different than a previous study of researcher practices on returning genetic research results, which showed that 24% of researchers actually returned results to participants, with a further 28% offering to return results (Heaney *et al*., 2010). However, the authors pointed out limitations in that study including its small sample size (n=105) and possible response bias such that those who were more familiar with the topic were more likely to participate. They speculated that this may have led to a higher estimate of return of genetic research results than is accurate, which would explain the discrepancy in the findings of the two studies. Additionally, though the sample size in the current study was larger, the low response rate indicates a potential lack of generalizability in the results, and the study asked the question about the behavior of the return of results differently than did the current study.

One of the main findings of the current study was that the extent of interaction with participants was associated with the return of genetic research results. While it is not possible given the design of the study to determine the causality of this relationship, we can hypothesize how the two factors are related. One possibility is that those with more interaction with their participants view fewer barriers to returning results, making it practically easier to return results. Given that the extent of interaction was not related to perceived ethical obligation, it is unlikely that the more interaction, the more researchers felt a duty to return. Instead, it is likely that they either find it easier to return or they

structured the amount of interaction to facilitate return, potentially as one of the goals of the study.

Previous research on returning genetic research results found that researchers with an M.D. were more likely to have returned IRRs to their participants (OR 5.6). In addition, researchers of studies on children were more likely to return IRRs (OR 2.7). The authors speculated that researchers with medical degrees have a closer relationship with their participants, which could underlie this observed association (Heaney *et al*., 2010). This is in line with the finding that research with a more clinical context is associated with higher perceived ethical obligation to return results.

In the absence of consistent guidelines, researchers' perceived obligations are likely to have a strong influence on decisions about returning results. Additionally, factors related to their own research including extent of interaction with participants, the type of results that are generated, and factors outside of the research such as IRB influences, are related to the behavior. Our findings suggest that perceptions of ethical obligation are among the important considerations when researchers are deciding whether to return IRRs and IFs. Future studies could help to elucidate the details of the decision-making process including the main drivers of the decision whether and how to return genetic results to research participants.

Many researchers in this study are not returning results to their participants. Reasons for this decision varied, the most common being not generating results perceived to warrant return, followed by IRB or consent constraints, and the inability to re-contact participants. Previous studies have similarly identified barriers related to views that preliminary or "invalid" results as not deemed worthy of return, as well IRB constraints

or CLIA certification, and not considering the issue at all (Heaney *et al*., 2010). In our study, only 9.6% of researchers who do not return results reported that the reason was that they had not considered the issue. This is lower than previous work, which showed that 38-46% had not thought about it (Rigby and Fernandez, 2005; Heaney *et al*., 2010). This difference may suggest that researchers are becoming more familiar with this issue and giving it consideration.

Researchers in this study were likely working on a variety of types of studies including WES/WGS, nextgen sequencing, and genome-wide association study protocols. This may explain the difference between the relatively higher number of researchers returning results compared to those in Ramoni and colleagues (2013), who found that only 4% of authors of genome-wide association studies had returned results to their participants. The researchers in the current study that indicated that they do not return results to their participants because they "do not generate results that warrant return" may be referring to the type of results that are generated (WES/WGS versus GWAS). Thus, the type of research being conducted, as well as the potential results that may come from it, are likely important factors in the decision about whether to return results.

Previous studies have described the role that other entities have on the decision to return results, showing that the choice is not made solely by the researcher (Klitzman *et al*., 2013). The current study showed that for those who do not return results, 33% report IRB or consent constraints as one of the major factors in their decision. However, IRBs do not have consistent policies or guidelines themselves, leaving room for inconsistent practice driven in part by different researchers' perspectives on the context of their own

study and of the extent of their perceived ethical obligation. One study of United States IRB policies regarding the return of research results showed that the majority had no policy on the issue, and less than a quarter of existing policies addressed results from genetic research specifically (Kozanczyn *et al*., 2007). Given a lack of guidelines, researchers are one of the key players in current decisions about whether to return genetic research results to participants.

Ethical obligation to return genetic research results, while a distinct concept from legal obligation, is nevertheless related in terms of practical implications. Pike and colleagues argue that in the current context of a lack of legal precedent, legal obligation will be determined by how researchers act on their perceived ethical obligation (2014). Pike and colleagues called for consensus about practice and consent documents that disclose how incidental findings will be handled.

As Pike and colleagues argued in the context of genetic IFs, researchers must make decisions about how they will return all genetic results at the outset of their study, and make corresponding consent documents that outline the approach. These documents, they say, will become the basis for court decisions about legal liability (2014). In addition to this practical connection to future legal obligation, including this information in the consent process is an ethically sound endeavor that forces transparency so that participants know what to expect when deciding whether or not to participate in a specific research study.

Currently, there is no consistent and widely used guideline or set of guidelines about the return of genetic research results (IRRs and IFs) to research participants. Instead, it is up to researchers, along with *ad hoc* committees and IRBs, to decide on the

issue. Previous work has shown that researchers support the involvement of a number of stakeholders in the decision about whether to return results including IRBs, research participants, and PIs (Klitzman *et al*., 2013). Our data suggest that practice is related to the extent of interaction with research participants as well as perceived obligation to return research results by researchers. In the absence of other guidance, researchers are making their own decisions, highlighting the need for policies. Practice guidelines should address consent practices related to return of results as well as parameters for making decisions in practice. Overall, the field needs more deliberate decision-making with all interested parties.

In addition to more transparent consent processes by individual researchers, it is also clear that there is a need for additional guidelines on the return of genetic research results in the research community. Three in four survey respondents agreed or strongly agreed that guidelines on returning results are unclear or inconsistent. There is great deal of variability in how researchers are approaching this issue. While it is not feasible to consider a single set of guidelines that will work for everyone given the wide variety of research contexts in genomics, there is an obvious need for a more deliberate and consistent approach to the topic that proactively considers the obligations that researchers have to their participants (both ethical and legal) and advances the collaborative research enterprise.

Limitations

While these data provide insights into how human genetics researchers are thinking about obligations to return results to their participants, there are several

limitations to be considered. First, this analysis was based on a cross-sectional research design, which does not allow for the identification of causal relationships. It does provide a snapshot of how a sample of researchers are currently thinking about obligation and the practice of return of results, and is a concrete examination of how a bioethical framework can be used to better understand practice.

A key limitation is the low response rate. It is possible that the researchers who answered the survey hold different views than those who did not. They may perceive higher ethical obligation and have more active reporting practices, or the opposite may be true. Overall, the existence and direction of any response bias is difficult to elucidate. There is no immediate reason to assume the sample is biased towards or against those who would return results or perceive an ethical obligation to do so. Participants were recruited to respond to a survey on four major human subjects issues in human genetic research, all of which registered as salient among respondents; we would not therefore expect strong opinions about return of results to be the only motivating force behind participation in the survey [Appendix 2 and 3]. Because the response rate is low, the estimate of researcher opinions is unlikely to be a precise one. Yet our sample size was 358, and the data provide insight into a possible association between perceptions of ethical obligation and reported return of results. In a larger more representative sample, it would be unlikely that the observed correlations would disappear, but it may be that additional associations would have been observed.

Practical Implications

It is clear that the research endeavor is at a crossroads on a global level about the return of genetic research results to participants. This research shows that the decision about the return of research results lies not with current guidelines or laws, but rather with individual researchers and teams. Indeed, 74% of respondents in this study agreed or strongly agreed that guidelines on returning results are unclear or inconsistent, and there is great deal of variability in how researchers are approaching this issue. As described above, researchers are often not making decisions about the return of results on their own. For instance, decisions can be influenced by other research team members and by IRBs. Understanding researchers' views on their obligations is important for everyone with a role in the research process including researchers, participants, policymakers, nurses, and genetic counselors.

For genetic counselors, who may be involved directly on the research team or indirectly through other related bodies such as IRBs, these data can inform practice. On a more global scale, understanding the factors associated with the practice of return of results in research can help inform genetic counselors' involvement in institutional policymaking and participation in crafting research protocols. One of the major roles that genetic counselors play in research is in consenting participants. As described above, transparent informed consent processes on all protocols are crucial to a productive relationship with research participants. Thus, incorporating a discussion of how researchers view the relationship with participants (and the associated practical question of whether they return genetic research results) alongside a discussion of what participants are hoping to get out of a particular research project is an important part of

truly “informed” consent. Overall, understanding the extent to which perceived obligation by the researcher translates into actual practice can also help genetic counselors involved in research to more effectively partner with research teams and can inform individual interactions with participants.

APPENDIX 1: Survey

Genetics & Public Policy Center
Survey of Human Genetic Researchers and Biobank Leaders
Draft November 11, 2013

Eligibility page
Thank you for agreeing to participate in this survey. Before continuing, we must first confirm your eligibility.

Your completion of this survey will serve as your consent to be in this research study.

Please enter the personal code found in your email invitation. [Fill in code]

Opt-out page

Thank you. To opt out of receiving any further reminders about this survey, please enter the personal code found in your email invitation. [Fill in code]

[E1] Are you age 18 or older?

Yes

No

[IF NO] Thank you for your interest. Unfortunately, you are not eligible to complete the survey. [EXIT SURVEY]

[E2] Are you based in the United States?

Yes

No

[IF NO] Thank you for your interest. At this time we are surveying only U.S.-based researchers. [EXIT SURVEY]

[E3] Are you an undergraduate or graduate student, or a post-doctoral researcher?

Yes

No

[IF YES] Thank you for your interest. Unfortunately, you are not eligible to complete the survey. [EXIT SURVEY]

[E4] Is your main area of research related to ethical, legal, social or policy issues surrounding genetics?

Yes

No

[IF YES] Thank you for your interest. Unfortunately, you are not eligible to complete the survey. [EXIT SURVEY]

[E5] Is one of your main areas of work human genetic or genomic research?

Yes

No

[E6] Are you a senior staff member of a biobank (or biorepository) supporting human genetic research?

For the purposes of this survey, an eligible biobank is defined as a structured resource used at least in part for the purpose of genetic research that meets all of the following criteria:

- U.S.-based collection of human individuals' samples and data
- Samples must include one or more of the following: cells, blood, plasma, saliva or other tissue used to derive DNA and genotype information, DNA, RNA, or sequence data
- At least some phenotypic information must be linked to the samples
- Samples and/or data are made available to support research on genetic, genomic, proteomic, or metabolomic determinants of health or medicine

EXCLUDED from this study are biobanks collected for non-research purposes, such as diagnostics, forensics, transplantation, transfusion audits, and marketing authorization.

Yes, I am senior staff at a biobank that meets the criteria above.
No, I am not.

[IF E5=No and E6=No] Thank you for your interest. Unfortunately, you are not eligible to complete the survey. [EXIT SURVEY]

[IF E5=YES AND E6=NO, THEN E7 = RESEARCHER; SKIP to 1]
[IF E5=NO AND E6=YES, THEN E5 = BIOBANK LEADER; SKIP to 1]

[IF E5=YES AND E45=YES, THEN ASK E6]

[E6] You indicated that you are both a researcher focused on human genetics as well as senior staff of a biobank or biorepository that supports genetic research. For the purposes of this survey, in which you will be asked about informed consent, data sharing, the privacy of research participants, and the return of individual research results, do you feel you are most experienced speaking as a researcher or as the leader or administrator of your biobank?

Human genetics researcher
Biobank/biorepository leader or administrator

Introduction

You are eligible to take the survey. Thank you again for your interest.

This survey, conducted by the Johns Hopkins University Genetics and Public Policy Center with funding from the National Human Genome Research Institute, is collecting information from genetic researchers and biobank leaders about a number of issues related to the use of samples and data from human subjects.

This survey is being distributed to human genetics researchers and to managers and directors of biobanks and biorepositories. You may have received this invitation from more than one source. Please complete the survey only once.

If you are involved in multiple biobanks or research studies, please answer the questions focusing on the study or biobank with which you are most closely involved.

The survey is being administered by the firm GfK. All of the information you provide in this survey will be kept in strict confidence by GfK. No identifying information will be collected and stored. Data collected during the survey will be used only in the aggregate and will not identify any particular researcher, institution or biobank. During the survey, you will be given the option to authorize re-contact by GfK for follow-up interviews. No re-contact will be initiated unless the Johns Hopkins IRB approves a separate study protocol.

This survey will take approximately 20 minutes to complete. After completing the survey, you will be offered a choice of receiving a $10 gift card to Amazon.com or having a $10 donation made to either the American Society of Human Genetics Trainee Award fund or the International Society for Biological and Environmental Repositories travel award fund.

Demographic and Descriptive Information

[1] Approximately how many individuals have provided samples or data for your biobank or research study? Again, please focus on the study or biobank with which you are most closely involved.

1-100
101-200
201-500
501-1,000
1,001-5,000
More than 5,000

[IF RESEARCHER]
[2R] What types of research do you conduct? (Check all that apply)

Clinical genetic research
Basic human genetic research
Bioinformatics research
Other (please specify) [FILL IN]

[IF RESEARCHER]
[4R] Does your main area of research focus on:
A single disease, trait or condition?

A group of diseases, traits or conditions (e.g., cancer, cardiovascular disease)?
A broad range of phenotypes?
My research is not disease-focused

We are interested in the sources of the data and samples you use in your research.

[6] Do any of your data or samples come from a clinical population?
Yes
No

[IF RESEARCHER, THEN ASK 7R and 8R]

[7R] Do you use samples or data that you collected directly from participants?

Yes
No

[8R] Do you use samples or data collected by other researchers?

Yes
No

[SKIP TO [10]

[10] What is the nature of your interaction with research participants? (check one)
We have no contact information on our participants
We have the ability to re-contact participants but have not done so
After initial samples and data are collected we have no further contact with participants
We have some contact with our participants after initial sample and data collection
We regularly interact with research participants

Return of Research Results

The next section of the survey focuses on returning individual genetic research results and incidental findings to study participants. Individual genetic research results are findings that are directly related to the topics of research. Incidental findings are results obtained in the process of genetic testing or sequencing that are deemed medically significant that are unrelated to the topics of research.
[Provide hyperlinked definitions: Individual genetic research result; Incidental finding]

First, we would like to know about your practices with respect to returning results.

[28] Do you return [individual genetic research results] to participants? (check one)
a. We do not return any genetic research results
b. We may return a research result if it is deemed important
c. Our protocol includes the return of one or more genetic research results
d. Our protocol does not specify whether we will return research results

[29] Do you return any genetic [incidental findings] to research participants? (check one)
a. We do not return any incidental findings
b. We may return an incidental finding that we deem important
c. Our protocol includes the return of one or more incidental findings
d. Our protocol does not specify whether we will return incidental findings

[IF CHECK 28b, 28c, 29b, or 29c, THEN ASK 30-33; ELSE SKIP TO 48]

[IF CHECK 28a or 29a, THEN ASK Q34, ELSE SKIP to OPINIONS/BELIEFS]

[34] Why did you decide not to return research results or incidental findings? [check all that apply]

- We did not think about returning results
- We will not generate results that warrant return
- We did not want to return results
- We were not able to return results because of the constraints of our consent or IRB
- We were not able to return results because we cannot re-contact participants
- We did not return results because we do not have the clinical expertise or resources
- Other [fill in]

OPINIONS / BELIEFS

Now we'd like to ask you some questions about your opinions regarding the return of research results.

[35] Do you agree or disagree with the following statement? [Strongly agree / Agree / Disagree / Strongly Disagree / Don't know]
I do not support returning individual genetic research results or incidental findings to participants.

[36] Do you agree or disagree with the following statements about obligations to return results? [Strongly agree / Agree / Disagree / Strongly Disagree / Don't know]

- I have no obligation to return individual research results
- I have no obligation to return incidental findings
- I have no obligation to look for medically significant variants unrelated to the topics of research.

[38] Do you agree or disagree with the following statements? [Strongly agree / Agree / Disagree / Strongly Disagree / Don't know]

- Guidelines on returning results are unclear or inconsistent
- Returning results and incidental findings could expose researchers and biobanks to legal liability
- Researchers are not equipped to return results responsibly
- The financial costs of returning results are prohibitive

[77] What is your primary work setting?
University/Academic
University/Clinical
Other clinical
Other non-profit
Biobank
Government
For-profit industry
Other (please specify)

[79] What is your age?
18-30
31-40
41-50
51-60
61-70
71-80
81+

[80] What is your gender?

Male
Female

[81] Have you ever been a participant in biomedical research?
Yes
No

[82] Have you ever served on an Institutional Review Board (IRB)? [Y, N]

[83] Does your institution have an IRB? [Y, N, DK]

[84] Does your study or biobank have an advisory board, ethics committee or review board other than an IRB? [Y, N, DK]

[85] Which of the following funding source(s) sponsor your primary research or biobank? [check all that apply]

National Institutes of Health
Other federal agency/agencies
State or local governments
Private foundation (e.g., Wellcome Trust, Robert Wood Johnson)
Industry
Other

INCENTIVE PAGE

Thank you very much for your participation. All survey participants will be entered into a raffle to win one of five Amazon Kindles.

In appreciation of your time and effort, please select one of the following: [select one]

- A $10 Amazon.com gift card (An email address is required. Email addresses will be kept separate from survey responses).
- [if ISBER=1 then offer:] a $10 donation to the International Society for Biological and Environmental Repositories travel award fund
- [if ASHG=1 or IF IDCODE VALUES = 30000-50000 then offer] a $10 donation to the American Society of Human Genetics Trainee Award fund

[IF YES TO AMAZON.COM GIFT CARD]
Please enter the email address where you wish to receive your gift card: [_____]

THANK YOU PAGE - 3 OPTIONS

[IF ASHG DONATION] Thank you very much for your participation. A donation will be made to the American Society of Human Genetics trainee award fund.

[IF ISBER DONATION] Thank you very much for your participation. A donation will be made to International Society for Biological and Environmental Repositories travel award fund.

[IF GIFT CARD] Thank you very much for your participation. An Amazon.com gift certificate will be sent to the email provided within one week.

If you have any questions or problems related to this survey, please contact Dave Kaufman, the principal investigator, at 202-265-1673, or the Johns Hopkins Medicine Institutional Review Board at 410-955-3008.

APPENDIX 2: Initial ASHG Recruitment Letter

Dear [ASHG MEMBER]:

The American Society for Human Genetics (ASHG), on behalf of the Genetics and Public Policy Center at Johns Hopkins University, is delighted to invite you to participate in a research study survey of U.S. genetic researchers about their practices and opinions related to human subjects issues in the conduct of genetic research.

A number of recommendations about informed consent, data sharing, privacy protection, and the return of research results have been published recently. This study will document and quantify how researchers are addressing these issues in the field, their opinions about outstanding challenges, and their preferences for additional guidance.

The Johns Hopkins University School of Medicine Institutional Review Board (IRB) has approved this research project. The survey will be administered online by GfK, a well-regarded research firm. If you agree to take this survey, all of the information you provide will be kept in strictest confidence, and the Genetics and Public Policy Center, GfK, and ASHG will not be able to identify individual responders or link individual identifying information to survey responses.

To complete the survey, please go to the following website and enter the personal code below.

[www.xxxxxxxxxxxx.com]

Personal code: [XXXX]

We anticipate that it will take about 20 minutes to complete the survey. You have until XXXX, 2014, to complete the survey. In recognition of your time, the Genetics and Public Policy Center will offer the first 300 survey participants the choice of a $10 gift certificate to Amazon.com or a $10 donation to the American Society of Human Genetics Development Fund, which assists with trainee travel costs to the annual ASHG meeting. In addition, everyone who completes the survey will be entered into a raffle to win one of five Amazon Kindles.

If you do not wish to participate in the survey and do not want to receive a reminder email, please click this link and enter the personal code above:
[www.xxxxxxxxxxxx.com]

We thank you for your help with this research. If you have any questions regarding the survey you can contact GfK at xxx@gfk.com or Dave Kaufman at the Genetics and Public Policy Center (202-235-1673 or dkaufma2@jhu.edu).

Sincerely,

APPENDIX 3: ASHG Survey Reminder
Subject: Reminder to Participate in a Johns Hopkins Study on Human Genetics Research

Dear [ASHG MEMBER]:

This is a reminder that you have been invited to participate in a research survey being conducted by the Genetics and Public Policy Center at Johns Hopkins University to gather opinions from U.S. genetic researchers about informed consent, the return of research results, privacy, and data sharing. We are writing again to invite you to take part in this important research project before XXXX, 2014.

We know your time is valuable. Your opinions will directly inform the development of guidelines and tools to streamline research while minimizing harm to participants.

To complete the survey, please click on the link below and enter the following personal code:
Personal code: [XXXX]
[www.xxxxxxxxxxxx.com]

We anticipate that it will take about 20 minutes to complete the survey. You have until XXXX, 2014, to complete the survey. In recognition of your time, the Genetics and Public Policy Center will offer the first 300 survey participants the choice of a $10 gift certificate to Amazon.com or a $10 donation to the American Society of Human Genetics Development Fund, which assists with trainee travel costs to the annual ASHG meeting. In addition, everyone who completes the survey will be entered into a raffle to win one of five Amazon Kindles.
The survey has been approved by Johns Hopkins University Institutional Review Board. The survey will be administered online by GfK, a well-regarded research firm that will keep your responses in strictest confidence. None of your survey responses will be linked to any personally identifying information. The Genetics and Public Policy Center, GfK and ASHG will not be able to identify individual responders.

We thank you for your help with this research. If you have any questions regarding the survey you can contact GfK at xxx@gfk.com or Dave Kaufman at the Genetics and Public Policy Center (202-235-1673 or dkaufma2@jhu.edu).

Sincerely,

REFERENCES

Beskow, LM. (2007). Considering the nature of individual research results. *The American Journal of Bioethics* 6(6): 38-40.

Beskow, LM and Burke, W. (2010). Offering Individual Genetic Research Results: Context Matters. *Science Translational Medicine* 2(38).

Bollinger JM, Scott J, Dvoskin R, Kaufman D. (2012). Public preferences regarding the return of individual genetic research results: findings from a qualitative focus group study. *Genetics in Medicine* 14: 451–457.

Bookman EB, Langehorne AA, Eckfeldt JH *et al*. (2006). Reporting genetic results in research studies: Summary and recommendations of an NHLBI Working Group. *American Journal of Medical Genetics* 140A: 1033–1040.

Brandt, D.S., Shinkunas, L., *et al*. (2013). A closer look at the recommended criteria for disclosing genetic results: perspectives of medical genetic specialists, genomic researchers, and institutional review board chairs. *Journal of Genetic Counseling* 22(4): 544-553.

Council for International Organizations of Medical Sciences (CIOMS). (2002). International ethical guidelines for biomedical research involving human subjects. Available at: http://www.cioms.ch/publications/layout_guide2002.pdf

Clayton, E.W., Kelly, S.E. (2013). Let us ask better questions. *Genetics in Medicine*, 15(11): 871-872.

Cummings, SM; Savitz, LA; and Konrad, TR. (2001). Reported response rates to mailed physician questionnaires. *Health Service Research*, 35(6): 1347-1355.

Dressler LG, Smolek S, Ponsaran R, Markey JM, Starks H, Gerson N, Lewis S, Press N, Juengst E, Wiesner GL. (2012). IRB perspectives on the return of individual results from genomic research. *Genetics in Medicine,* 14: 215-22.

Fabsitz RR, McGuire A, Sharp RR, et al. (2010). Ethical and practical guidelines for reporting genetic research results to study participants: updated guidelines from an NHLBI working group. *Circulation: Cardiovascular Genetics* 3:574–580.

Facio, FM; Brooks, S; Loewenstein, J; Green, S; Biesecker, LG; and Biesecker, BB. (2011). Motivators for participation in a whole-genome sequencing study: Implications for translational genomics research. *European Journal of Human Genetics*, 19(12): 1213-1217.

Facio, FM; Eidem, H; Fisher, T; Brooks, S; Linn, A; Kaphingst, KA; Biesecker, LG; and Biesecker, BB. 2013. Intentions to receive individual results from whole-genome

sequencing among participants in the ClinSeq study. *European Journal of Human Genetics* 21: 261-265.

Fernandez C.V., Strahlendorf C., Avard D., Knoppers B.M., O'Connell C., Bouffet E., Malkin D., Jabado N., Boycott K., Sorensen P.H. (2013). Attitudes of Canadian researchers toward the return to participants of incidental and targeted genomic findings obtained in a pediatric research setting. *Genetics in Medicine* Published online January 31, 2013.

Fischhoff, B. (2013). The sciences of science communication. *PNAS*, 110 (Supplement 3), 14033-14039.

Folger, Robert *; In:* Behavioral business ethics: Shaping an emerging field. De Cremer, David (Ed.); Tenbrunsel, Ann E. (Ed.); New York, NY, US: Routledge/Taylor & Francis Group, 2012. pp. 123-142.

Folger, R., Ganegoda, D., Rice, D., Taylor, R., and Wo, H. (2013). Bounded autonomy and behavioral ethics: Deonance and reactance as competing motives. *Human Relations* 66: 905-924.

Fullerton SM, Wolf WA, Brothers KB, Clayton EW, Crawford DC, Denny JC, Greenland P, Koenig BA, Leppig KA, Lindor NM et al. (2012). Return of individual research results from genome-wide association studies: experience of the Electronic Medical Records and Genomics (eMERGE) Network. *Genetics in Medicine* 14: 424-31.

Green, R.C., Berg, J.S., Grody, W.W., *et al*. (2013). ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Released by American College of Medical Genetics and Genomics; Mar 2013; Phoenix, Arizona. *Genetics in Medicine* 15: 565-574.

Haga, S.B. and Zhao, J.Q. (2013). Chapter Two- Stakeholder Views on Returning Research Results. *Advances in Genetics* 84: 41-81.

Hardimon M.O. (1994). Role obligations. *The Journal of Philosophy* 91(7): 333–363.

Heaney C, Tindall G, Lucas J, Haga SB. (2010). Researcher practices on returning genetic research results. *Genetic Testing and Molecular Biomarkers* 14: 821-7.

Institute of Medicine. 2001. *Crossing the quality chasm: A new health system for the 21st century*, Washington, D.C.: National Academy Press.

Manolio, TA. (2006). Taking our obligations to research participants seriously: Disclosing individual results of genetic research. *American Journal of Bioethics,* 6(6): 32-34.

McGuire, A.L., Knoppers, B.M., Zawati, M.H., and Clayton, E.W. (2014). Can I be sued for that? Liability risk and the disclosure of clinically significant genetic research findings. *Genome Research* 24(5): 719-723.

Meacham, M.C., Starks, H., Burke, W., Edwards, K. (2010). Researcher perspectives on disclosure on incidental findings in genetic research. *Journal of Empirical Research on Human Research Ethics* 5:31-41.

Meyer, MN. (2008). The kindness of strangers: The donative contract between subjects and researchers and the non-obligation to return individual results of genetic research. *The American Journal of Bioethics* 8(11): 44-46.

National Bioethics Advisory Commission. (1999). Research Involving Human Biological Materials: Ethical Issues and Policy Guidance. Rockville, MD. http://bioethics.georgetown.edu/nbac/human/oversumm.pdf.

O'Neill, O. "Duty and Obligation," in *Encyclopedia of Ethics*, ed. Becker, L.J. and Becker, C.B. (New York: Garland Publishing, 1992); Richard B. Brandt in Encyclopedia of Ethics, ed. Lawrence J. Becker and Charlotte B. Becker (New York: Garland Publishing, 1992), 278; and Richard B. Brandt, "The Concepts of Obligation and Duty," *Mind* 73 (1964): 374-393.

Partridge AH, Winer EP. (2002). Informing clinical trial participants about study results. *JAMA* 288:363–365.

Ramoni, R.B., McGuire, A.L., Robinson, J.O., Morley, D.S., Plon, S.E., Joffe, S. (2013). Experiences and attitudes of genome investigators regarding return of individual genetic test results. *Genetics in Medicine* 15(11): 882-887.

Ravitsky, V. and Wilfond, BS. (2006). Disclosing individual genetic results to research participants. *American Journal of Bioethics* 6(6): 8-17.

Rigby, H., Fernandez, CV. (2005). Providing research results to study participants: Support versus practice of researchers presenting at the American Society of Hematology annual meeting. *Blood* 106(4): 1199-1202.

Summit Series on Clinical Trials, Cancer Leadership Counsel, Cancer Research Foundation of American, Coalition of National Cancer Cooperative Groups, and the Oncology Nursing Society. 2000. Alexandria, VA. http://www.preventcancer.org/healthyliving/clinicaltrials/summit.cfm.

United Nations Educational, Scientific and Cultural Organization (UNESCO). 2003. International declaration on human genetic data. Available at: http://www.unesco.org/new/en/social-and- human-sciences/themes/bioethics/human-genetic/data/

Wolf SM, Lawrenz FP, Nelson CA, et al. (2008). Managing incidental findings in human subjects research: analysis and recommendations. *The Journal of Law, Medicine & Ethics* 36(2): 219–248, 211.

Wright, M.F., Lewis, K.L., Fisher, T., Hooker, G.W., Emanuel, T., Biesecker, L., and Biesecker, B.B. Preferences for results delivery from whole exome sequencing/whole genome sequencing: Results from ClinSeq® focus groups. *Genetics in Medicine* 16(6): 442-447.

Caroline Young

Contact Information
Cell: (703) 893-4284
Email: caroline.young3@gmail.com

Address
1510 Emerson Avenue
Mclean, VA 22101

EDUCATION

2012-2015 Johns Hopkins University/National Human Genome Research Institute
Sc.M. Genetic Counseling expected May 2015

2007-2011 Kenyon College, Graduated May 2011, Bachelor of Arts, cum Laude
Distinguished Academic Scholarship Recipient
Major: Biology
Minor: Classical Civilization

2009 School For Field Studies, Kenya (Fall Semester Study Abroad)

2007 McLean High School, Valedictorian

GENETIC COUNSELING CLINICAL EXPERIENCE

Genetic Counseling Intern

-Howard County General Hospital Center for Maternal and Fetal Medicine, Columbia, MD
-GeneDx, Gaithersburg, MD
-Greater Baltimore Medical Center Cancer, Baltimore, MD
-Specialized Obstetrics and Gynecological Imaging, Brisbane, Australia
-Genetic Health Queensland, Royal Brisbane and Women's Hospital, Brisbane, Australia
-Virginia G. Piper Cancer Center, Scottsdale, AZ
-Walter Reed National Military Medical Center, Bethesda, MD
-ClinSeq, NHGRI, NIH, Bethesda, MD
-NIAID, NIH, Bethesda, MD
-NHGRI, NIH, Bethesda, MD
-NHGRI Policy and Program Analysis Branch, NIH, Bethesda, MD

COUNSELING AND COMMUNICATION

2011-2012 Counseling and Advocacy Intern, DC Rape Crisis Center, Washington, DC
-Provided crisis counseling over the telephone to rape survivors and secondary survivors (friends and family).
-Developed updates to volunteer training materials and referral guide.
-Researched additional counseling tools and psychological tests to be employed by counselors.

Spring 2010-Fall 2010 Peer Advice Counselor, Kenyon College
-Counseled other students on the phone and through instant messaging about academic and personal concerns.

Summer 2010 Intern, Genetic Alliance, Washington, DC
-Developed research paper on the role of prenatal educators in newborn screening to justify a partnership between Genetic Alliance and an internationally-renowned professional society.
-Analyzed federal advisory committee deliberations and correspondence to craft resource for newborn screening professionals on the nomination and evaluation criteria for adding conditions to the recommended uniform screening panel.
-Conducted background literary research and analysis for federal grant applications and national publications to maintain ongoing funding opportunities and image for Genetic Alliance.

RESEARCH AND TEACHING

2009-2010 Research Assistant, Laboratory of Dr. Karen Hicks, Kenyon College (2 Semesters)
-Aided in genetics research on *Arabidopsis thaliana* to examine how day length affects flowering and mutations in the pathway of flowering regulation.

Spring 2009 Teaching Assistant, Introductory Biology Lab, Kenyon College
-Assisted students in conducting experiments during lab periods and writing scientific papers based on their reports.
-Helped students design and conduct original experiments.

Summer 2008 Teacher's Assistant, Potomac School Summer Camp
-Assisted in developing and carrying out lesson plans for elementary school children in science class.

SELECTED CONFERENCE PARTICIPATION

2014 National Society of Genetic Counseling, Poster Presenter
-"Perceived Obligations by Researchers in Genetics to Return Individual Research Results and Incidental Findings to Participants"

2010 Advancing Novel Partnerships, staff
-Genetic Alliance's annual conference.

2010 5th Annual Genetics Day on the Hill, group leader
- Educating congressmen about issues important to the genetics community.

2010 2nd Annual Gene Screen, staff
-A night of film on health and genetics in conjunction with Genetic Alliance's annual conference.