To Return or Not to Return? IRB Perspectives on Obligations to Return Genetic Incidental Findings to Research Participants

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters.

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Citable link</td>
<td><a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:15821579">http://nrs.harvard.edu/urn-3:HUL.InstRepos:15821579</a></td>
</tr>
<tr>
<td>Terms of Use</td>
<td>This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA">http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA</a></td>
</tr>
</tbody>
</table>
ABSTRACT

Purpose: Whether researchers have an obligation to disclose genetic incidental findings (GIFs) to research participants has been widely debated in the literature, but the debate has lacked empirical data. This is the first extensive national examination of IRB professionals’ understanding, experience, and beliefs surrounding GIFs in the context of genomic sequencing.

Methods: We conducted a cross-sectional online survey of 796 individuals sampled from the membership of Public Responsibility in Medicine and Research (PRIM&R) about background and experience with GIFs and ethical reasoning supporting or diminishing an obligation to disclose.

Results: Most participants have had experience dealing with GIFs (74%), but less than half (47%) felt well prepared to evaluate a plan for managing them. Respondents generally agreed (78%) that researchers have some obligation to disclose GIFs. The top-cited ethical principles supporting this obligation were a duty to warn (84%), respect for autonomy (80%), and beneficence (79%). While a majority believed that the obligation could be undermined by inadequate clinical or analytical validity (72%) or inadequate clinical utility (66%), respondents disagreed that researchers’ additional time and effort (87%) and participants’ imperfect understanding of genetics (70%) were valid reasons for non-disclosure. Almost all (96%) indicated it is definitely or probably acceptable for a participant to elect not to receive any GIFs. This view, however, became less pronounced (63%) when asked to respond to specific case studies.

Conclusion: Most IRBs are actively dealing with GIFs but feel only moderately prepared to do so. Although a majority of respondents believes there is sometimes or always an obligation to disclose and that duty to warn, autonomy, and beneficence are guiding forces in this obligation, there is still not complete consensus. Respondents generally rejected instrumental and paternalistic concerns as valid reasons for non-disclosure.
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glossary</td>
<td>4</td>
</tr>
<tr>
<td>Introduction</td>
<td>5</td>
</tr>
<tr>
<td>Materials &amp; Methods</td>
<td>14</td>
</tr>
<tr>
<td>Results</td>
<td>16</td>
</tr>
<tr>
<td>Discussion and Suggestions for Future Work</td>
<td>19</td>
</tr>
<tr>
<td>Summary and Conclusions</td>
<td>26</td>
</tr>
<tr>
<td>References</td>
<td>27</td>
</tr>
<tr>
<td>Tables &amp; Figures</td>
<td>32</td>
</tr>
<tr>
<td>Appendix</td>
<td>38</td>
</tr>
</tbody>
</table>
GLOSSARY OF ABBREVIATIONS

ACMG = American College of Medical Genetics
CLIA = Clinical Laboratory Improvement Amendments
GIF = genetic incidental finding
HNPPCC = Hereditary Non-Polyposis Colon Cancer
IF = incidental finding
IRB = institutional review board
NBAC = National Bioethics Advisory Commission
NHGRI = National Human Genome Research Institute
NIH = National Institutes of Health
PCSBI = Presidential Commission for the Study of Bioethical Issues
PRIM&R = Public Responsibility in Medicine and Research
INTRODUCTION

A person agrees to participate in a research study involving genomics. She donates her DNA via blood sample, and along with many others, her DNA undergoes whole genome sequencing by the researchers. In the midst of performing their research analysis, the researchers discover that this patient has a genetic variant putting her at increased risk for Alzheimer’s Disease. What, if any, obligation do they have to disclose this finding to the study participant? What is the ethical reasoning to either support or reject that obligation?

The above is just one example of the challenges posed by genetic incidental findings in research. Genetic incidental findings (GIFs) are individual genetic results generated in the course of research that are unrelated to the aims of the research, but which may have clinical, reproductive, or personal significance for participants.\(^1\) One of the first examples of a GIF that helped bring the topic to light was the discovery of non-paternity in the course of establishing family pedigrees.\(^2\) Now, with the rapid expansion of genetic technologies, the range of genetic findings that could have personal implication for participants has significantly widened. As these sequencing technologies are becoming increasingly powerful and affordable research tools,\(^3\) large-scale whole genome and whole exome studies raise questions about how best to manage a broad range of possible GIFs.\(^4\)

There has been an active debate about the circumstances, if any, under which there is an obligation for researchers to disclose GIFs to research participants.\(^5,6,7,8\) Despite widespread recognition of the importance of this question, decisions about disclosure of GIFs are typically determined locally, with no nationally accepted guidelines to direct researchers or institutional review boards (IRBs).\(^9,10\)

In the past, common precedent had been simply to inform participants that they would not receive any GIFs, aligning with the National Bioethics Advisory Commission’s (NBAC) 1999 recommendation advising against disclosure.\(^11\) Over the years, however, there has been a shift toward recognizing the non-feasibility of this stance given the greater volume and accessibility of research results. The literature has also documented a shift in ethical reasoning in favor of offering to disclose a certain set of findings that meet a certain standard of validity, severity, and actionability.\(^1,5,6\) However, the ethical reasoning to support this obligation, along with its scope and limitations, remains unclear. Moreover, as researchers identify IRBs as the appropriate authority in questions regarding disclosure, ascertaining the background, expertise, and beliefs of this group will inform the ongoing debate.
A brief history of incidental findings

The concept of incidental findings (IFs) and the debate on whether to return them is neither new nor specific to genetics research. The subject has been addressed in clinical scenarios dealing with both genetic and non-genetic findings. It has also been discussed in the research setting with regard to non-genetic results, such as if a mass is found with a brain MRI or inflammatory bowel disease picked up during CT colonography.

In the radiology research setting, studies have reported IF prevalence rates of 13% to 84% with brain MRIs. There was similarly wide variation in how such IFs are handled. In one survey of MRI laboratories, 36% reported that all findings are disclosed after being read by a neuroradiologist; 47% reported disclosure only with suspicious findings; and 13% reported no disclosure at all. More generally, it has been found that few institutional guideline and professional society documents explicitly address managing IFs in research; and even when the subject is addressed, the terms used to describe IFs are not consistent across documents.

When dealing with non-genetic incidental findings in research, many have spoken out in favor of at least some obligation to disclose. An ethical analysis by Wolf et al. asserted that researchers have an obligation to address the possibility of discovering IFs in IRB communications, research protocols, consent forms, and communications with participants during the recruitment process. In December 2013, the Presidential Commission for Study of Bioethical Issues (PCSBI) released an in-depth report on IFs entitled Anticipate and Communicate. One of their key recommendations was that study participants be informed about the possibility of research IFs, along with how those findings will be disclosed, before the start of participation. The report also emphasized the importance of informed consent, calling open communication and clear consent documents between researchers and study participants essential.

While much of the ethical analysis on non-genetic IFs has informed the debate on GIFs, questions have been raised about whether GIFs are fundamentally different. That is, can the same ethical analyses in neuroimaging also guide decision-making in genetics? Genetics research on humans is currently quite broad, including association studies, examination of allele frequencies, and studies of natural selection, human migration, and genetic variation. Some have drawn attention to a deeply embedded uncertainty with GIFs because of genetics’ inherent reliance on probability to understand risk information. As Van Ness asks, “Is there an obligation to inform a
research participant of findings despite their lack of precision?”

Clayton also draws attention to archived samples in genomics research, leading to the possibility of the “cold call”: “This is not like research on functional magnetic resonance imaging (fMRI) or computed tomography (CT) colonography in which people at least know they have been in a scanner.” These comments reference the fact that genetics research often involves archived samples where participants may not know or remember the blood draw that collected their DNA, what it was used for, or that research on the samples is ongoing.

When it comes to returning genetic findings in a clinical (that is, not research) setting, an important step forward was made in 2013 when the American College of Medical Genetics (ACMG) released a landmark paper offering guidelines for disclosure. Laboratories performing clinical sequencing should seek and report mutations of certain specified classes, the report recommended. Some examples included BRCA1 and BRCA2 genes for hereditary breast and ovarian cancer and certain genes implicated in Familial Adenomatous Polyposis, Lynch syndrome, Marfan syndrome, and familial hypercholesterolemia. The group also recommended the creation of an ongoing process for updating these recommendations at least annually as new information is learned on penetrance and clinical utility. Of note, in their conclusions they commented explicitly on the limitations of applying their conclusions to GIFs in a research setting, stating: “Although we hope that investigators find our process and these recommendations useful in their attempts to design thresholds and lists for the return of genomic findings to research participants, we did not design this list for that purpose.”

Thus, while ethical analyses and guidelines on incidental findings in non-genetics research settings and genetic clinical settings may offer some guidance in thinking about GIFs in research, there do exist certain differences as outlined above that demand a more nuanced analysis, tailored to resolve the question at hand.

Ethical perspectives on the obligation to return: a theoretical framework

At the heart of debate on whether researchers have an obligation to return GIFs is a fundamental question about the role of a researcher. Do researchers have an obligation to provide individual benefits from their work, or is their role strictly to generate knowledge to help society at large? Both extremes of these perspectives – along with various positions in the middle – have been articulated in the debate.
On one end of the spectrum, some reject an obligation to return GIFs for inappropriately focusing on the individual’s best interest over creating generalizable information. An obligation to return, they say, conflates research and therapy – a distinction that “already bedevils investigators and research participants alike.” The idea that research and therapy should be clearly distinguished can be traced back to the Belmont Report, the cornerstone of many IRB decisions that outlines the basic ethical principles governing conduct for human subjects research. The report makes clear that in research, there is no guarantee of benefit to the subject, whereas in therapy, the patient has an expectation of benefit. This position was used to support the initial guidelines of the NBAC in 1999, which stated that individual results should generally not be offered to study participants. Conflating research and therapy could harm participants by misleading them into believing that the research’s primary role is therapeutic (an idea known as “therapeutic misconception”); meanwhile, a related concern is that researchers might oversell the benefits of enrollment.

There exist other ethical objections beyond conflating research and therapy. Some critics point out that since the research is not intended to provide individual benefits, the results available might be preliminary, which could incite unnecessary anxiety or false reassurances. In many cases, research continues to be done in laboratories that are not CLIA approved, indicating that these labs are not specifically authorized for testing for the purposes of medical prevention, diagnosis, and treatment. Others worry about the potential misallocation of limited scientific resources, burdens on the research infrastructure, or that disclosure is simply not feasible given that researchers are typically not trained to deliver this kind of information.

Clayton specifically rejects that the ethical principle of respect for persons requires an obligation to return findings; rather, she argues, informing participants about what they can and cannot access through the study truly shows respect for persons by increasing transparency in research.

On the other side, some argue that genetic findings should be disclosed to participants if they meet particular conditions and that it is simply unethical to withhold potentially beneficial information from individuals because of an arbitrary divide between research and therapeutic settings. Fernandez et al called disclosure an “ethical imperative,” and the ethical principles of respect for persons, beneficence, autonomy, reciprocity, duty to rescue, and justice have all been invoked to support the obligation. In addition to providing information that could improve individuals’ quality of life, either clinically or personally, returning results could have other benefits, such as enhancing trust in research, emphasizing participants’ contribution to
understanding disease, and improving public understanding of genetics. Some have also argued that the blurring of research and clinical care already occurs, or that it is not necessarily negative if appropriately recognized.

Ravitsky et al. characterizes the arguments at the opposing ends of the spectrum as the *research-focused approach* versus the *autonomy-focused approach*, and the authors instead propose an alternative framework somewhere in between. The *result-evaluation approach*, as they call it, may or may not disclose results depending on the nature of the information generated by the study and on the context of the study. They argue that this approach is comprehensive because it allows researchers and IRBs to consider numerous relevant factors. According to their approach, the nature of the information that should be considered includes analytic validity (that is, accuracy and reliability of the data) and clinical utility (information that can be used to improve a participant’s well-being). They also acknowledge that information with personal, and not necessarily clinical, significance may sometimes be returned. Examples of genetic information with personal benefit include information related to ethnic or cultural identity, or genetic variations associated with behavior traits such as addiction. The authors justify returning this information if certain factors in the “context” of the study support disclosure. These factors that ought to be considered, they argue, include investigator capabilities (such as quality control in the laboratory and ability to communicative effectively, such as with genetic counselors), whether a participant can access results via other means, and the relationship between the researcher and the participants. The authors assert that with reciprocity a guiding ethical principle in the obligation to return, a more involved relationship between researcher and participant increases the obligations of the former toward the latter.

Ravitksy et al are not alone in taking an approach that supports an obligation to return given certain conditions. Beskow et al has also argued for a middle-ground approach, contending that a “one-size-fits-all” model should not apply to decisions about returning individual results. Instead, researchers and IRBs should consider the level of entrustment involved in the research, the intensity and duration of interactions with participants, and the dependence of the study population. The debate shows that opinion seems to be moving toward this middle ground, where there is some obligation to disclose a limited set of findings that meet an exacting standard of validity, severity, and actionability. Yet even within this group, defining the contours of the obligation remain hazy.
A call for guidelines

In the face of disagreement about the relative merits of these different positions, one thing that has been generally agreed upon is the need for formal guidance documents outlining criteria and procedures for disclosure. In their 2012 report on privacy and progress in whole genome sequencing, the PCSBI acknowledged the importance of developing such guidelines, pointing out that even while participants might desire results, this alone is not a sufficient reason to disclose them given the need for accuracy. As a result, they recommended that “Funders of whole genome sequencing research should support studies to evaluate proposed frameworks for offering return of incidental findings and other research results derived from whole genome sequencing.”

Some groups have made headway toward this goal. The National Heart, Lung, and Blood Institute Working Group convened in 2004 and then again in 2009 to propose guidelines for returning results. The group recommended that a genetic finding should be offered to study participants if it 1) has important health implications for the participant, with the associated risks established and substantial, 2) the genetic finding is actionable, meaning there are established therapeutic or preventive interventions available, 3) the test is analytically valid, and 4) participants gave informed consent to receive results. The National Human Genome Research Institute (NHGRI) has also offered some guidelines, reporting that “[r]esearch participants should have access to experimental research data except when…the research results are of unproven clinical validity, and the IRB has judged that there is no benefit to the research subjects.”

In addition, a 2-year project funded by the NIH and published in Nature in 2012 analyzed the responsibilities involved in managing GIFs in a biobank research system and recommended that findings that are analytically valid, reveal an established and substantial risk of a serious health condition, and are clinically actionable should generally be offered to consenting contributors. When re-identification of participants is possible, the authors asserted, the biobank has four core responsibilities: to clarify the criteria for evaluating findings, to analyze the finding, to re-identify the participant, and to re-contact him or her to offer the result.

The empirical approach

In the midst of the ethical debate, there has been growing recognition for the role of empirical research in shaping the normative discussion. From participants’ perspective, there is a
body of evidence documenting participants’ interest in receiving GIFs. Historically, research participants have expressed interest in receiving results even if the data are upsetting or not considered clinically useful. The literature is now increasingly recognizing the value of ascertaining the experience and beliefs of the other major parties involved – namely, researchers and IRB members.

Why is this? First, knowing which ethical principles key stakeholders find justifiable can help focus the ethical debate by steering the discussion away from theoretical arguments that are not actually employed. This may ultimately help frame the debate in a way that more closely mirrors reality. In addition, understanding how people are practically dealing with the dilemma of whether there is an obligation to return individual genetic research results – including their experiences, background, and training – can help tailor formal training and guidelines toward specific identified areas of weakness or uncertainty.

With researchers looking to external sources for guidance, the perspectives of IRB professionals in particular have become increasingly sought after. As IRBs are obligated to ensure that researchers have plans to protect the rights and welfare of human subjects, along with managing “unanticipated problems,” these committees serve as reasonable sources of guidance for researchers grappling with questions of whether to disclose GIFs. IRB members already have a history of wrestling with incidental findings in areas of research outside genetics, and studies show researchers identify IRBs as the appropriate authority in questions regarding disclosure. In 2007, the National Institutes of Health (NIH) Policy for Sharing of Data on genome-wide association studies recommended that IRBs determine policies to assess the appropriateness of returning individual findings to research participants.

Since then, several empirical studies have looked into IRB professionals’ understanding and beliefs regarding GIFs. These studies indicate an acceptance of some duty to disclose individual genetic research results, given certain circumstances. In 2011, Simon et al. reported on the perspectives of 34 IRB chairs, finding that 96% had no knowledge of IRB requirements regarding GIFs and informed consent. They also found that chairs put emphasis on the consent process in addressing how to handle incidental findings, yet they were concerned about making the consent process more complex, dealing with participants’ changing preferences over time, and conveying the inherent uncertainty of genetic results. The following year, Dressler et al. conducted interviews with 31 IRB professionals and found that many were not comfortable with their expertise in genomics research. There was also a general lack of experience in addressing
return of results. Those surveyed agreed that guidelines would be helpful, and they also generally agreed that GIFs should be returned to research participants when results are medically actionable and participants desire to know them. Finally, another 2012 study found that IRB chairs were in general agreement about the need for a plan regarding disclosure of GIFs included in the informed consent process. In the absence of such a plan, they believed that research participants should make their own decisions about whether they would want to receive GIFs. Some IRB professionals, however, favored overriding a subject’s wishes if medical opinion determined that disclosure or nondisclosure would be better for the participant. Taken together, these studies suggest that although there is some basis for IRBs’ support of disclosure, the reasoning, scope, and practical duties surrounding that obligation remain unclear.

Assessing the perspectives of researchers has revealed just as much complexity. In 2010, Heaney et al. found that 54% of genetics researchers considered the issue of returning results. The most common factors guiding their decisions were whether the results were clinically useful (18%) and the notion of respect for participants (13%). Interestingly, those with MD’s were significantly more likely to offer to return results compared to researchers with just PhD’s. Another 2010 study by Meachem et al. conducted semi-structured interviews with researchers who were asked to respond to a vignette about discovering incidental findings of clinical significance. Based on the responses received, the authors recommended several actions that can prepare researchers to make more informed decisions, including clarifying the possibility of incidental findings in consent forms and developing procedures to communicate results and provide follow-up. Finally, a 2014 survey looked at how researchers decide what findings to return. They found top influences include information about the gene variant, concerns about participants’ well-being, and input from external entities such as principal investigators, IRBs, and/or professional organizations.

**Innovation of current research**

We conducted the first extensive national examination of IRBs professionals’ understanding, experience, and beliefs surrounding GIFs in the context of genomic sequencing. Prior studies have tended to focus on results generated from genome-wide association studies, which are less likely to produce GIFs as compared to whole genome and whole exome sequencing. Additionally, prior studies have tended to examine viewpoints qualitatively, via interviews with limited numbers of subjects. Our goal was to capture, quantitatively and on a
broader scale, how the research ethics community thinks about the management and disclosure of GIFs in the context of genomic sequencing protocols.

Specifically, we developed and administered a nationwide survey to explore IRB professionals’ perspectives on whether there is an obligation to return individual genetic results, the ethical principles that the research ethics community appeals to in support of such an obligation, and the reasons that might diminish such an obligation. We also explored how views on incidental findings vary across demographic characteristics such as professional training.

With this work, we have captured the voice of influential actors who play a direct role in setting local policy on disclosure. By elucidating IRB members’ working knowledge, experience, and perspectives on ethical issues surrounding genetic incidental findings, this work may ultimately inform the normative debate, along with guiding practical recommendations for improving the review process.
MATERIALS AND METHODS

Study Participants and Survey Distribution

We conducted a cross-sectional online survey of individuals (data collected in late 2012) sampled from the membership of Public Responsibility in Medicine and Research (PRIM&R), a national nonprofit organization comprised of individual and organizations involved in a variety of kinds of human subjects research. Its membership includes IRB members and other IRB professionals, in addition to researchers and government staff. The survey, created with web survey software Qualtrics, was piloted using a small cohort of research ethics scholars prior to its wide distribution. A link to a self-administered electronic survey consisting primarily of multiple-choice questions, with some opportunity for short answer, was emailed to 2,288 members of PRIM&R who had previously self-identified as having a specific interest in human subjects protections. Participants were provided with $5 pre-incentive. The response rate was calculated in accordance with the definition RR2 from the American Association for Public Opinion Research36; therefore, only partial and complete surveys counted as responses. With 796 completed surveys received, the response rate (RR2) was 34.8%.

Survey Instrument

Participants were introduced to the subject through a brief synopsis about the possibility of GIFs being generated from whole genome and whole exome sequencing (Figure 1). Participants were also provided definitions of key terms used through the survey (next-generation sequencing, genetic incidental finding, clinical significance, actionability, genome, exome, variant, and clinical and analytical validity). The survey consisted of questions addressing several domains: 1) background and experience with GIFs, 2) reasons supporting an obligation to disclose GIFs, 3) reasons that diminish an obligation to return GIFs, and 4) right not to know.

Respondents who expressed a belief that researchers have an obligation to disclose GIFs to research participants were asked about reasons supporting that obligation. All respondents, regardless of how they answered that initial question, were asked about reasons that diminish an obligation to return GIFs. Participants indicated the strength of their agreement with various statements on a five-point Likert scale. Participants were also given an “other” option where they were given space to write additional reasons of their own. Participants were then presented
with hypothetical scenarios involving various types of GIFs and study protocols and responded whether there was an obligation to disclose the GIF or whether the study should be approved.

Finally, the survey assessed demographic characteristics, background and experience with GIFs, and beliefs about additional guidance. Respondents also completed an 8-item genetic literacy scale adapted from a validated scale by Kaphingst, et al.$^37$

**Data Analysis**

Survey data was exported from Qualtrics, and survey responses were analyzed with descriptive statistics (percentages for discrete responses, means and standard deviations for continuous responses). Summary statistics were calculated using Stata 13. Differences among groups’ responses were calculated by IRB voting status, genetics literacy score, educational level, primary role on the IRB (clinical, scientific, and all others), and combined primary and secondary IRB roles (clinical primary or secondary role; scientific, but not clinical; and not clinical or scientific). Chi-square tests were used to evaluate percentages of respondents who agreed or disagreed with the reasoning statements. Confidence intervals for the proportions were calculated and compared using a two-tailed t-test for differences. Differences with \( p<0.05 \) were considered statistically significant.
RESULTS

Respondent characteristics

Of survey respondents who provided demographic information, the majority identified as female (74%) and non-Hispanic white (88%) (Table 1). These characteristics are largely consistent with those found in survey research on similar IRB-affiliated populations. The subject pool was generally well-educated, with most respondents (67%) holding a masters or doctorate degree. When asked about primary or secondary professional roles, 17% of respondents reported holding a clinical position and 43% identified holding a scientific position.

Most respondents (91.6%) reported having served on or been affiliated with an IRB. Of these respondents, 99% had been involved with an IRB for at least one year, and 36% had been involved for more than 10 years. Of the respondents who identified their current or most recent affiliation role with an IRB, 492 (68%) identified as holding a non-voting position, and 235 (32%) identified as serving as a voting member of the IRB. Of the voting members, 111 (15%) reported filling a chair or vice-chair role. Other voting members reported being scientific members (9%), non-scientific members (5%), community members (2%) and unspecified members (1%). Non-voting affiliates were primarily staff/administrators (60%); the rest (8%) filled other roles such as quality assurance and regulatory compliance.

The majority of our participants (74%) reported that they have had experience dealing with GIFs, suggesting that their responses to the survey were informed by actual experience (Table 2). The subjects expressed moderate confidence in their understanding of the ethical issues raised by GIFs (19% very confident, 52% somewhat confident, 35% slightly confident). Participants reported slightly lower confidence in their genomic knowledge (9% very confident, 36% somewhat confident, 35% slightly confident). This self-assessment was in line with their genetic literacy scores, which was assessed using a validated questionnaire. Most of the subjects (73%) had received some training about GIFs, though among those about half (37%) described the training as a little. About half of all participants (47%) felt at least somewhat well prepared to grapple with GIFs.

An obligation to disclose GIFs

In general, respondents held the position that researchers have some obligation to disclose GIFs to participants. The majority (65%) indicated that there was “sometimes” an obligation to disclose GIFs; 13% thought there was “always” an obligation, and another 13%
thought there was “rarely” an obligation. Only 2% believed there was never an obligation, and 7% did not know.

Ethical reasoning

Respondents were divided when asked about the ethical principles that might support an obligation to disclose GIFs (Table 3). The principle with the strongest support was a duty to warn, with 84% of respondents either strongly agreeing or agreeing that researchers should disclose GIFs because of a duty to warn participants if they are in significant, imminent danger. Other principles that were widely supported included respect for autonomy of participants (80% of respondents strongly agreed or agreed) and beneficence (79% strongly agreed or agreed). As a cross-check, the participants were asked to rank the top three principles that supported an obligation to disclose GIFs. The top-cited principles remained beneficence, respect for autonomy, and duty to warn (Figure 2).

Respondents were more divided on other principles, including professional responsibility (67% strongly agreed or agreed, 23% strongly disagreed or disagreed), a need to maintain public trust in research (58% agreed, 32% disagreed), a need to maintain an institution's professional reputation (36% agreed, 52% disagreed), a need to treat research participants like clinical patients (34% agreed, 54% disagreed), and reciprocity (34% agreed, 56% disagreed). Even though professional responsibility and public trust in research garnered more than 50% agreement, close examination of the top three ranking reasons reveals that support for these principles is consistently lower than support for duty to warn, beneficence and autonomy. The former two principles received a much lower percentage of first and second place rankings.

Finally, a number of participants indicated that they were unsure about certain principles. Most significantly, 18% percent were unsure about whether a concern for legal liability supported an obligation to disclose, and 13% were unsure about whether participants' right to know their own genetic information supported an obligation to disclose.

There were only two potential factors that respondents strongly endorsed as possibly diminishing an obligation to disclose GIFs (p<0.05) (Table 4). Almost three-quarters of respondents (72%) either agreed or strongly agreed that inadequate clinical and analytical validity of the genetic screening information could undermine this obligation. Similarly, a majority (66%) either strongly agreed or agreed that inadequate demonstrated clinical utility of the genetic risk information could also undermine an obligation. For the other factors considered,
respondents did not believe they negatively affected an obligation to disclose GIFs. Most significantly, 87% of respondents either disagreed or strongly disagreed that the additional time and effort required for the researcher to disclose GIFs was great enough to reduce an obligation to do so. Most respondents (73% disagreed or strongly disagreed) did not support the idea that clinical researchers have different responsibilities than practicing physicians and thus do not have an obligation to disclose GIFs. Respondents generally also did not accept (70% disagreed or strongly disagreed) that participants are not likely to understand genetic risk information sufficiently to disclose GIFs, and did not agree (67% disagreed or strongly disagreed) that the potential psychological impact on participants of learning their genetic risk information is too high. Finally, 57% of respondents disagreed or strongly disagreed that there is a lack of funding, resources or infrastructure to disclose GIFs.

*Right not to know*

Almost all respondents (96%) indicated that it is either definitely acceptable or probably acceptable for a participant to elect *not* to receive any GIFs. This opinion, however, was inconsistently expressed when the question was applied to specific case studies. Case A involved a participant who had chosen not to receive any GIFs, but whose research team had identified genetic evidence of Hereditary Non-Polyposis Colon Cancer (HNPCC, a serious and actionable disease). In this case, 26% of respondents replied that the researchers should definitely or probably disclose this finding, 63% replied that researchers should definitely not or probably not disclose this finding, and 11% were unsure. Case B was similar to Case A, but here the original participant was deceased and researchers were debating whether to contact the participant's family to inform them about this potentially significant information. In this case, 51% of respondents believed that researchers should definitely or probably contact the family, 35% thought that researchers should definitely not or probably not contact the family, and 14% were unsure.
DISCUSSION AND SUGGESTIONS FOR FUTURE WORK

Discussion

Questions about whether researchers have an obligation to disclose GIFs have been widely debated in the literature. This is the first extensive national survey empirically examining IRB professionals’ understanding of GIFs and beliefs about an obligation to disclose GIFs. Our data demonstrate that a majority of IRB professionals believe that researchers do have a duty to disclose GIFs to research participants. Underlying this perspective are a broad range of opinions about the ethical underpinnings of a duty to disclose GIFs and the various considerations that may or may not limit such a duty.

When the research ethics community began exploring questions relating to incidental findings, genomic sequencing technology was in its infancy. The turn around time from obtaining blood to obtaining results was long, the cost prohibitive, and the meaning of much of the information uncertain. There were real questions about the frequency with which researchers would generate results that would be meaningful to individual participants. Unsurprisingly, given recent advances in sequencing power, our data suggests that most IRBs are actively dealing with GIFs; this is no longer a theoretical problem. Our participants’ responses were generally influenced by actual experience grappling with GIFs, with three-quarters of respondents indicating some experience with discussing incidental findings raised in research.

However, given that IRBs are grappling with the incidental findings problem, it appears that they are only moderately prepared. Although 73% had received some training about GIFs, about half of these (36%) described this training as “a little.” Moreover, while a majority (71%) were very or somewhat confident about their knowledge of the ethical issues they raise, many respondents seemed to need additional information about genomic science. Only 47% were very or somewhat confident about their genomic knowledge. Overall, respondents reported that they were only moderately prepared to deal with issues raised by GIFs, with less than half (47%) indicating that they were very well prepared or somewhat well prepared. Only a bit over half (55%) indicated that the training they received helped somewhat or a lot in reaching a clearer understanding of ethically advisable ways to manage GIFs.

To what extent do IRBs believe there is an obligation to disclose GIFs?

Our survey began with a threshold question about whether there is a general obligation to offer incidental findings to participants. Although a majority (78%) of study respondents agreed
that there was sometimes or always an obligation to disclose GIFs, our data indicate that there is still not a complete consensus on this issue. Importantly, there was a minority of respondents (15%) who felt that there was either rarely or never an obligation to disclose GIFs. This may reflect a general uncertainty or apprehension about the state of genomic science and clinical genomics, a supposition supported by the majority of participants who agreed that a mistrust of scientific accuracy and clinical utility were factors that may reduce an obligation to disclose GIFs.

We had hypothesized that views on the existence of an obligation to disclose incidental findings would vary by professional training (e.g., MD versus PhD) and role (e.g., clinical versus scientific). As a fundamental difference between research and therapy duties has been widely discussed in the theoretical literature as a reason not to disclose, it would make sense that those with more pure research (and less clinical) backgrounds might be less supportive of a duty to disclose. This would also be in line with a prior study looking at researcher perspectives, which found that those with MD’s were significantly more likely to offer to return results compared to researchers with only PhD’s. However, our findings showed no statistically significant differences between MDs and PhDs and those who considered their roles clinical versus scientific, suggesting that IRB professionals’ beliefs seem to be less influenced by their formal training.

What ethical reasons are cited in support of an obligation to disclose GIFs?

There has been an active debate about the circumstances, if any, under which there is an obligation for researchers to disclose GIFs to research participants, with little consensus. This lack of agreement might stem from the fact that there has been little clarity about the principle(s) on which such obligations might rest; the contours of an obligation will necessarily shift depending on the underlying principle(s) one puts forward. In order to learn more about how IRBs are thinking through the incidental findings problem, we asked survey participants about the principles that they endorse in support of an obligation to disclose GIFs. While IRB members’ views on the most convincing principles in support of an obligation to disclose GIFs are not, of course, dispositive proof of the correct normative view, such data can provide insight into the lines of reasoning that are more and less employed by those directly involved.

There was no single dominant principle that emerged, which is perhaps unsurprising given the array of disparate arguments presented in the literature. The three ethical principles that
most participants felt supported an obligation to disclose GIFs were 1) a duty to warn; 2) respect for autonomy; and 3) beneficence (see Table 3, Figure 2). Although these principles can all be used to defend an obligation to disclose GIFs, they can conflict in the breadth of their obligation. For example, relying on a duty to warn principle may only require disclosing GIFs that represent significant risk of a serious disease, while beneficence may suggest that all potentially useful or relevant GIFs be disclosed. Similarly, basing this obligation on participant autonomy might suggest returning all GIFs and allowing participants to decide for themselves which ones are most important. Again, we had hypothesized that professional training and role would be correlated with different principles, but this did not turn out to be the case.

Support was quite limited for a number of instrumental justifications in support of an obligation to disclose, suggesting that our study population found broad philosophical principles more persuasive. Only about a third of respondents agreed with the idea that maintaining an institution's professional reputation and avoiding legal liability supported an obligation to disclose GIFs. Interestingly, a relatively large percentage of respondents (19%) were uncertain about whether a concern for legal liability supported an obligation to disclose GIFs, perhaps due to the lack of existing case law. It is possible that views on this rationale for disclosure of GIFs might shift as legal precedent evolves, particularly if the actual risk of liability increases substantially.

Additionally, about a third (34%) of respondents agreed or strongly agreed that an obligation to disclose GIFs rests on a belief that research participants should be treated like clinical patients. This number was surprisingly high, given that since the start of the debate, a fundamental difference between therapy and research has been pointed to by multiple ethicists as a foundational reason not to disclose.\textsuperscript{10,11,16-18} That one-third of IRB professionals disagrees with this distinction indicates that this theory is perhaps less important in practice than the theoretical literature suggests. The lack of support among two-thirds of participants may lend credence to concerns raised about applying to the research realm the ACMG' guidelines for disclosing certain GIFs in the context of clinical genomics.\textsuperscript{15,40}

The other principle that respondents disagreed with most strongly (56% either disagreed or strongly disagreed) was reciprocity between researchers and participants, or the idea that researchers should disclose GIFs because they owe participants something in exchange for their contribution to the research endeavor. This support for the principle of reciprocity was surprisingly low, given that it is often cited in the literature in support of an obligation to disclose
GIFs, suggesting that these arguments have less traction in the way that IRBs think about the incidental findings problem. A significant portion of IRB respondents were also unsure about whether an obligation to disclose GIFs is supported by an inherent right of research participants to know their own genetic information, possibly indicating that survey respondents do not believe research participants have such a right. This was also surprising, given that prior research has shown that from study participants’ perspective, most are interested in receiving IFs, even when the information is considered not clinically useful or has the potential to be upsetting.25-27 Thus, though we did not compare the beliefs of IRB professionals and participants directly, our findings suggest that there may be a disconnect between participants’ and IRB professionals’ thinking on this matter.

Limitations of an obligation to disclose GIFs

When asked about the factors or circumstances that could potentially undermine an obligation to disclose GIFs, respondents largely found many of the suggested factors unconvincing. In particular, respondents rejected excuses such as a lack of resources to disclose GIFs or the burden of additional time and effort required to do so, both of which are pointed to within the literature as significant obstacles to declaring a broad obligation to disclose.21,41 Respondents agreed only that inadequate clinical or scientific information reduces an obligation to disclose GIFs. Since both of these factors are based on the current state of science and clinical medicine, it is possible that as the evidence base develops this opinion may change.

Survey respondents also rejected excuses based on paternalistic concern for research participants, reaffirming the data indicating that an obligation to disclose GIFs rests at least partly on respect for participant autonomy. Over two thirds of respondents (70%) disagreed that an obligation to disclose GIFs is undermined by a worry that participants are not likely to understand genetic risk information, and 67% of respondents disagreed that the potential psychological impact on participants of learning their genetic risk information is too significant to disclose GIFs.

Interestingly, 73% of participants either disagreed or strongly disagreed with the idea that the unique role of the clinical investigator, and particularly the lack of clinical responsibilities equivalent to those of practicing physicians, excuses researchers from disclosing GIFs. This seems to indicate that respondents believe clinical researchers should behave similarly to physicians, again in disagreement with the literature that points to the therapy/research
distinction as a major reason not to disclosure. Interestingly, however, respondents largely rejected the idea that research participants should be treated like clinical patients. The source of this inconsistency in beliefs about the difference between research and clinical care is not clear, and it may complicate efforts to evaluate GIF disclosure policies within clinical research protocols.

*Right not to know*

The question of whether research participants have a “right not to know” certain genetic information about themselves continues to be a controversial issue, particularly after the release of the ACMG recommendations suggesting an “opt out” option offered to patients for clinical genome sequencing.\(^{42,43,44}\) It is clear from our data that while respondents may have strong beliefs about this right in theory, in practice their views are more complicated. Almost all respondents indicated that it is definitely or probably acceptable for a participant to elect not to receive any GIFs, but this strong consensus wavered in the face of a specific case. When considering Case A, in which a research team found a highly significant and actionable GIF in the genomic data of a research participant who had elected not to receive any GIFs, a full quarter of respondents said that the research team should either definitely or probably disclose the GIF anyway. In Case B, where the original research participant was deceased but had similarly elected not to receive any GIFs, half of respondents thought the research team should either definitely or probably contact the participant's family. The data supporting these case studies are consistent with the strong consensus that an obligation to disclose GIFs rests on a duty to warn participants who are in significant, imminent danger. Perhaps another element driving these results is concern about the nature of informed consent and whether research participants truly understand the meaning and implications of not receiving GIFs. It is important, then, for the research ethics community to come to a clear consensus about whether there is truly an absolute right for participants not to know any genetic information about themselves. It is also vital to address this issue in conversations about informed consent, as these results suggest we may need to change the process of consent to have a second discussion about the significance of findings once results are obtained. Holding an inconsistent position in this area could potentially compromise participant trust in research, as well-meaning researchers disclose information to participants who had previously elected not to receive it.
Study Limitations

Our study has several important limitations. First, our response rate was moderate, and nonresponse bias may affect the generalizability of the results. Second, it is possible that subjects were influenced by social acceptability bias. There has been significant discussion about incidental findings, and the field has been moving towards a view that there is an obligation to disclose some set of findings, which could have influenced what respondents thought was the desirable answer. Third, our sample was not exclusively comprised of IRB members and was also disproportionately female. While it is possible that IRB professionals could hold different views from IRB members, or men from women, we found no statistically significant differences between these groups given our sample size. Furthermore, we believe our study population is appropriately representative of the human subjects research ethics community since they were drawn from PRIM&R, the preeminent organization for the research ethics profession. Fourth, we found very few differences by professional training or role but this could have been due to the small size of some of these subgroups. Finally, this is a rapidly moving field, so this data should be viewed as a snapshot of opinions held in late 2012.

Suggestions for Future Work

This research represents the first extensive national examination of IRB professionals’ understanding, experience, and beliefs surrounding GIFs in the context of genomic sequencing. By ascertaining IRB members’ working knowledge and perspectives on ethical issues surrounding GIFs, this work may ultimately help focus the normative debate in a way that more closely mirrors scientific reality. However, the conclusions from this research have also generated some additional questions that would benefit from further study.

One avenue of such research is determining, in more detail, how IRB professionals feel about the distinction between research and therapy. While this distinction has been widely cited in the theoretical literature as a justification for non-disclosure, our results suggest that IRB professionals perhaps do not agree. Still, these results were somewhat inconsistent. For example, while a majority (73%) disagreed that the unique role of the investigator excuses researchers from disclosure, only 34% agreed that research participants should be treated like patients. Based on these results, it is unclear precisely how IRB professionals view the investigator-participant relationship, and how that relationship affects the obligation to return GIFs. Given that the
research-therapy distinction is so prevalent in the literature, this empirical finding would benefit from further study to help hone whether, and in what capacity, the theoretical objection holds.

Another surprising result generated from this research was inconsistency over the right not to know. While the majority agreed with this principle in theory, their views diverged when presented with specific anecdotes. It is possible that one factor driving these results is concern about the nature of informed consent, including the idea that participants might not truly understand what they are consenting to, so that their consent may be overridden in certain circumstances. It would be valuable to tease apart what exactly those circumstances are in order to find an internally cohesive line of reasoning to support nuanced guidelines. For example, perhaps these results suggest a need to have a two-tiered consent process, where there is a second discussion with participants about whether they would want a certain finding only after that finding is obtained. A clearer understanding of how IRBs and researchers think about this issue can ultimately help us form guidelines to which the relevant parties can adhere. On a similar note, it would be valuable to directly compare beliefs of all relevant stakeholders – IRB professionals, researchers, and participants – on the issues addressed in this survey toward developing such guidelines.

Finally, from this research further questions have arisen about the logistics and limitations surrounding the obligation to return GIFs. While respondents generally rejected instrumental and paternalistic concerns as valid reasons for non-disclosure, it is unclear what is informing these beliefs. This research raises additional questions about the nature of the informed consent process, who should provide financial resources (given that lack of finances was rejected as a valid reason for non-disclosure), who should provide guidance on return of results, and the length of the obligation. It is also worth studying the scope and limitations of the obligation to return GIFs when the quality of the results might be less certain, such as if generated from a laboratory that is not CLIA-certified.
SUMMARY AND CONCLUSIONS

The debate about genetic incidental findings has been vigorous and continues to evolve, but it has lacked in-depth empirical data about the deliberative processes being used to oversee management in the research setting, even as IRBs are perceived as the relevant source of guidance on this issue. This study is the first extensive national examination of how IRB professionals are grappling with the ethical issues presented by the massive amount of data generated by genomic research. Our research indicates that IRBs are actively engaged with this problem, but like the rest of the field, have not yet reached comfortable stasis.

In particular, this work has shown that most IRBs are actively dealing with GIFs but feel only moderately prepared to do so. Although a majority believes there is sometimes or always an obligation to disclose and that duty to warn, autonomy, and beneficence are guiding forces in this obligation, there is still not complete consensus on this obligation. Respondents generally rejected instrumental and paternalistic concerns as valid reasons for non-disclosure. Moreover, a clear distinction between research and therapy, often cited in the theoretical literature, was not well supported by our participants’ answers. Though a majority believed that participants have a right not to know, views diverged on overriding this right when applied to specific cases. In general, professional training (e.g. MD versus PhD) did not underlie any significant differences in participants’ beliefs.

An interesting question remains about who is driving the push to return GIFs: academic bioethicists, researchers, IRBs, research participants, or some external third party such as policy makers or funding agencies. Given the majority of respondents who think that return of GIFs is appropriate, and the apparent discomfort with arguments that might constrain a duty to return GIFs, our data suggests that IRBs might be one powerful force compelling researchers to disclose.

The debate on the obligation to return GIFs has greatly progressed in recent years. We believe this research generated a strong body of evidence from important stakeholders (namely, IRB professionals) that may ultimately help inform the normative debate and the development of guidelines on this issue.
REFERENCES


National Institute of Health (NIH). Points to Consider for IRBs and Institutions in their Review of Data Submission Plans for Institutional Certifications Under NIH’s Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS),


42 American College of Medical Genetics and Genomics. ACMG Updates Recommendation on "Opt Out" for Genome Sequencing Return of Results.


Table 1. Demographic characteristics of survey participants. N=796.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (Percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>576 (74%)</td>
</tr>
<tr>
<td>Male</td>
<td>202 (26%)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
</tr>
<tr>
<td>High school or less</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Some college</td>
<td>51 (6%)</td>
</tr>
<tr>
<td>College</td>
<td>208 (26%)</td>
</tr>
<tr>
<td>Masters</td>
<td>284 (35%)</td>
</tr>
<tr>
<td>Doctorate</td>
<td>248 (31%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>673 (88%)</td>
</tr>
<tr>
<td>African American</td>
<td>46 (6%)</td>
</tr>
<tr>
<td>Asian American</td>
<td>27 (4%)</td>
</tr>
<tr>
<td>American Indian</td>
<td>14 (2%)</td>
</tr>
<tr>
<td><strong>Time with IRB</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>10 (1%)</td>
</tr>
<tr>
<td>1-2 years</td>
<td>68 (9%)</td>
</tr>
<tr>
<td>3-5 years</td>
<td>154 (21%)</td>
</tr>
<tr>
<td>6-10 years</td>
<td>233 (32%)</td>
</tr>
<tr>
<td>10+ years</td>
<td>263 (36%)</td>
</tr>
<tr>
<td><strong>Role with IRB</strong></td>
<td></td>
</tr>
<tr>
<td>Chair or vice chair</td>
<td>110 (15%)</td>
</tr>
<tr>
<td>Scientific member</td>
<td>60 (8%)</td>
</tr>
<tr>
<td>Non-scientific member</td>
<td>34 (5%)</td>
</tr>
<tr>
<td>Community member</td>
<td>13 (2%)</td>
</tr>
<tr>
<td>Administrator</td>
<td>428 (59%)</td>
</tr>
<tr>
<td>Other</td>
<td>82 (11%)</td>
</tr>
<tr>
<td><strong>Professional role</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>135 (17%)</td>
</tr>
<tr>
<td>Scientific</td>
<td>342 (43%)</td>
</tr>
</tbody>
</table>
Table 2. Respondents’ experience with genetic incidental findings, including knowledge of genomics and ethics, former training, and preparedness. N=796.

<table>
<thead>
<tr>
<th>Experience with GIFs</th>
<th>N (Percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>532 (74%)</td>
</tr>
</tbody>
</table>

**Genomic knowledge**
- Very confident: 74 (9%)
- Somewhat confident: 288 (36%)
- Slightly confident: 276 (35%)
- Not at all confident: 156 (20%)

**Ethical knowledge**
- Very confident: 154 (19%)
- Somewhat confident: 416 (52%)
- Slightly confident: 177 (22%)
- Not at all confident: 47 (6%)

**Training for Managing GIFs**
- A lot: 43 (5%)
- Some: 252 (32%)
- A little: 285 (36%)
- None: 213 (27%)

**Preparedness for Evaluating Plan to Manage GIFs**
- Very well: 64 (8%)
- Somewhat well: 308 (39%)
- Slightly well: 247 (31%)
- Not at all: 173 (22%)
Table 3. Respondents’ beliefs in the ethical principles that support an obligation to return genetic incidental findings. N=796.

<table>
<thead>
<tr>
<th>Ethical principles in support of an obligation to disclose</th>
<th>Strongly agree or agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duty to warn</td>
<td>658 (84%)</td>
</tr>
<tr>
<td>Respect for autonomy</td>
<td>626 (80%)</td>
</tr>
<tr>
<td>Beneficence</td>
<td>615 (79%)</td>
</tr>
<tr>
<td>Professional responsibility</td>
<td>520 (67%)</td>
</tr>
<tr>
<td>Public trust in research</td>
<td>450 (58%)</td>
</tr>
<tr>
<td>Right to know</td>
<td>418 (54%)</td>
</tr>
<tr>
<td>Institutional reputation</td>
<td>278 (36%)</td>
</tr>
<tr>
<td>Legal liability</td>
<td>267 (34%)</td>
</tr>
<tr>
<td>Participants = patients</td>
<td>264 (34%)</td>
</tr>
<tr>
<td>Reciprocity</td>
<td>261 (34%)</td>
</tr>
</tbody>
</table>
Table 4. Respondents’ beliefs in factors that can diminish an obligation to return genetic incidental findings. N=796.

<table>
<thead>
<tr>
<th>Factors that can diminish an obligation to disclose GIFs</th>
<th>Strongly agree or agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate clinical or analytic validity</td>
<td>567 (71%)</td>
</tr>
<tr>
<td>Inadequately demonstrated clinical utility</td>
<td>523 (66%)</td>
</tr>
<tr>
<td>Lack of funding, resources or infrastructure</td>
<td>230 (29%)</td>
</tr>
<tr>
<td>Adverse psychological impact</td>
<td>185 (23%)</td>
</tr>
<tr>
<td>Participants will not understand</td>
<td>171 (22%)</td>
</tr>
<tr>
<td>Researchers ≠ clinicians</td>
<td>145 (18%)</td>
</tr>
<tr>
<td>Time and effort required</td>
<td>58 (7%)</td>
</tr>
</tbody>
</table>
Figure 1. Introduction to GIFs, presented to all survey participants before the start of the survey.

Perspectives on Genetic Incidental Findings

Introduction

The goal of this project is to better understand how the research ethics community thinks about the management and disclosure of genetic incidental findings (GIFs) in the context of genomic sequencing protocols.

Over the past few years, new genetic sequencing technologies have become much more affordable and accessible. As a result, many investigators have begun to sequence their subjects’ entire exomes and genomes as part of their research.

In the course of sequencing and analyzing this data, investigators will likely come across individual genetic findings that are unrelated to the aims of their research but that might have clinical or personal significance for their subjects. There has been an active debate about the circumstances (if any) under which there is an obligation for investigators to disclose these findings to participants.

This is a research project designed to learn more about how people in the research ethics community think about these issues. Your participation is voluntary and you may choose not to take part in the survey.
Figure 2. Most common ethical principles cited to support an obligation to return GIFs.

**Ethical Principles, top three ranking**

- Autonomy
- Beneficence
- Duty to warn
- Right to know
- Responsibility to inform
- Public trust
- Similar to patient
- Reciprocity
- Liability
- Institutional reputation

Legend:
- %Ranked 3
- %Ranked 2
- %Ranked 1
APPENDIX

Survey

Q1 Have you ever served on or been affiliated with an IRB?
☐ Yes
☐ No

Q2 For how many total years have you been (or were you) involved with an IRB?
☐ Less than one year
☐ 1-2 years
☐ 3-5 years
☐ 6-10 years
☐ More than 10 years

Q3 Which best describes your current or most recent role with your IRB?
☐ Chair or vice chair
☐ Scientific member
☐ Non-scientific member
☐ Non-affiliated (community) member
☐ Administrator/Staff
☐ Other ____________________

Q4 Have your previous IRB deliberations ever included discussions of any kind of incidental findings (not limited to genetic findings, e.g. may include findings from radiological imaging)?
☐ Yes
☐ No

Q5 What guidance does or did your IRB rely on when making decisions about how to manage genetic incidental findings? Please check all that apply.
Institutional policy
IRB policy
Consistent IRB practice (No official policy)
None
Other ____________________
Unsure
Q6 How confident are you in your understanding of the science of genomic research studies?
- Very confident
- Somewhat confident
- Slightly confident
- Not at all confident

Q7 How confident are you in your understanding of the ethical issues that might arise from genomic research studies?
- Very confident
- Somewhat confident
- Slightly confident
- Not at all confident

Q8 How well prepared do you feel to evaluate a plan for managing genetic incidental findings?
- Very well prepared
- Somewhat well prepared
- Slightly well prepared
- Not at all well prepared

Q9 How much training, education, or other guidance have you received about managing genetic incidental findings in ethically advisable ways?
- A lot
- Some
- A little
- None

Q10 Did the training, education or guidance help you reach a clearer understanding of ethically advisable ways to manage genetic incidental findings?
- Yes, a lot
- Yes, somewhat
- Yes, a little
- No, not at all

Q11 This section is aimed at understanding your familiarity with clinical genetics. Please indicate whether the following statements are true or false.
| Each of us has variations in our genes that make it more likely we will get certain diseases. | True | False | Not Sure |
| Genetic tests can be done to find out how a person will react to certain drugs. | True | False | Not Sure |
| A person's race and ethnicity can affect how likely they are to get a disease. | True | False | Not Sure |
| You can only inherit breast cancer from your mother's side of the family. | True | False | Not Sure |
| A healthy person can carry a gene for a disease. If they have a child with someone who also carries a gene for the same disease they have a 50% risk of having an affected child. | True | False | Not Sure |
| If you have a variation in a gene that can cause cancer, there is nothing you can do to prevent getting cancer. | True | False | Not Sure |
| All women would benefit from getting a genetic test for breast cancer. | True | False | Not Sure |
| A mother always gives an X chromosome to her children but a father can give either an X or a Y chromosome to his children. | True | False | Not Sure |
Q12 Do you believe that researchers have an obligation to disclose genetic incidental findings to participants?
- Yes, always
- Yes, sometimes
- Rarely
- No, never
- I don't know

REASONS SUPPORTING AN OBLIGATION TO DISCLOSE INCIDENTAL FINDINGS
The following questions explore a number of ethical principles that could support an obligation to disclose genetic incidental findings in certain circumstances. Please read each statement and indicate how much you agree or disagree.
Q13 Researchers have an obligation to disclose genetic incidental findings…
<table>
<thead>
<tr>
<th>...because of beneficence, the idea that researchers should have the welfare of the research participant as a goal.</th>
<th>Strongly agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strong Disagree</th>
<th>Unsure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>...because of respect for autonomy, the recognition that all individuals have the right to make their own decisions.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>...because they have a duty to warn participants if the participants are in significant, imminent danger.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>...because research participants have an inherent right to know genetic information about themselves.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>...to maintain public trust in research.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>
...to maintain their institution’s professional reputation.  
...because they might be legally liable if a participant later develops a condition that could have been prevented.  
...because participants should be treated like patients, and clinicians would disclose these results to their patients.  
...because of a professional responsibility to inform their subjects.  
...because of a sense of reciprocity, or the idea that they owe participants something in exchange for their contribution to the research endeavor.
Q14 Other reasons why investigators have an obligation to disclose GIFs (please describe):

Q15 Of the ethical principles selected above that you believe support an obligation to return incidental findings, please rank the three most important. Drag your top three choices into the box on the right.

<table>
<thead>
<tr>
<th>Three most important</th>
</tr>
</thead>
<tbody>
<tr>
<td>_____ …because of beneficence, the idea that researchers should have the welfare of the research participant as a goal.</td>
</tr>
<tr>
<td>_____ …because of respect for autonomy, the recognition that all individuals have the right to make their own decisions.</td>
</tr>
<tr>
<td>_____ …because they have a duty to warn participants if they are in significant, imminent danger.</td>
</tr>
<tr>
<td>_____ …because research participants have an inherent right to know genetic information about themselves.</td>
</tr>
<tr>
<td>_____ …to maintain public trust in research.</td>
</tr>
<tr>
<td>_____ …to maintain their institution’s professional reputation.</td>
</tr>
<tr>
<td>_____ …because they might be legally liable if a participant later develops a condition that could have been prevented.</td>
</tr>
<tr>
<td>_____ …because participants should be treated like patients, and clinicians would disclose these results to their patients.</td>
</tr>
<tr>
<td>_____ …because of a professional responsibility to inform their subjects.</td>
</tr>
<tr>
<td>_____ …because of a sense of reciprocity, or the idea that they owe participants something in exchange for their contribution to the research endeavor.</td>
</tr>
<tr>
<td>_____ Other</td>
</tr>
</tbody>
</table>
REASONS THAT DIMINISH AN OBLIGATION TO DISCLOSE GENETIC INCIDENTAL FINDINGS
Q16 There may be reasons not to disclose GIFs that could override or diminish an obligation for investigators to disclose GIFs to individual participants. Please read each statement about these possible reasons and indicate how much you agree or disagree.
<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>The clinical and analytical validity (accuracy) of the genetic screening information is not adequate to disclose GIFs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The available genetic risk information does not have adequate demonstrated clinical utility (usefulness) to disclose GIFs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants are not likely to understand the genetic risk information enough to disclose GIFs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The potential psychological impact on participants of learning their genetic risk information is too significant to disclose GIFs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The additional burdens of disclosing GIFs on the researcher are too great.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
There is a lack of resources or infrastructure to support disclosing GIFs. Clinical investigators do not have the same kind of clinical responsibilities as practicing physicians; therefore, it is not necessary that they disclose GIFs.

Q17 Other reasons why an obligation to disclose GIFs may be diminished or nonexistent:

**INFORMED CONSENT & PROCEDURES FOR DISCLOSING GENETIC INCIDENTAL FINDINGS**
For the following questions, please choose the answer that best represents your perspective.

Q18 Research participants have a right not to know their own genetic information. In other words, it would be acceptable for them to choose not to receive any GIFs.
- Yes, it would definitely be acceptable
- Yes, it would probably be acceptable
- No, it would probably not be acceptable
- No, it would definitely not be acceptable
- Unsure

Q19 A participant has chosen on the consent form not to receive any GIF results. During its analysis, the research team finds evidence of high genetic risk for Hereditary Non-Polyposis Colon Cancer (HNPCC). The team believes this information will prevent serious disease and
perhaps even save the life of the participant. The team should disclose the finding, even though the participant indicated that he/she did not want to receive any GIFs.
☑ Yes, they should definitely disclose the finding
☑ Yes, they should probably disclose the finding
☑ No, they should probably not disclose the finding
☑ No, they should definitely not disclose the finding
☑ Unsure

Q20 A participant who elected on the consent form not to receive any GIF results has died during the course of the study. During its analysis of the deceased participant’s data, the research team found evidence of high genetic risk for Hereditary Non-Polyposis Colon Cancer (HNPCC). The team believes some of the participant’s family members may also have this risk, and the information could prevent serious disease and perhaps even save their lives. The consent form did not account for contact of family members of deceased participants. The team should contact the participant’s family members to let them know they have information that may be clinically useful to them, even though the participant him/herself did not want to receive the findings.
☑ Yes, they should definitely contact the participant’s family
☑ Yes, they should probably contact the participant’s family
☑ No, they should probably not contact the participant’s family
☑ No, they should definitely not contact the participant’s family
☑ Unsure