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Genomic Inheritances: Disclosing Individual Research Results From Whole-Exome Sequencing to Deceased Participants' Relatives

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Abstract

Whole-genome analysis and whole-exome analysis generate many more clinically actionable findings than traditional targeted genetic analysis. These findings may be relevant to research participants themselves as well as for members of their families. Though researchers performing genomic analyses are likely to find medically significant genetic variations for nearly every research participant, what they will find for any given participant is unpredictable. The ubiquity and diversity of these findings complicate questions about disclosing individual genetic test results. We outline an approach for disclosing a select range of genetic results to the relatives of research participants who have died, developed in response to relatives' requests during a pilot study of large-scale medical genetic sequencing. We also argue that studies that disclose individual research results to participants should, at a minimum, passively disclose individual results to deceased participants' relatives.

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Whole-exome sequencing and whole-genome sequencing (WES/WGS) are analytic tools that are being used with increasing frequency in genetic research. Unlike traditional candidate gene research, which looks only at targeted, relatively short portions of a research participant's DNA, WES/WGS gathers data from the entire set of gene coding regions across a research participant's genome (Ng et al. 2010). The cases presented here raised new variations on familiar questions that researchers will encounter as they begin generating significantly more information about research participants: Should genetic research results of potential clinical benefit be disclosed to a deceased participant's relatives? If so, under what circumstances and through what mechanism should they be disclosed? What subset of the results should be disclosed? It is this last question that is most pressing, as the scale of WES/WGS sequencing is unprecedented in clinical research.

This set of questions arose following the non-study-related death of a participant in ClinSeq, a study of large-scale medical genetic sequencing that aims to sequence and annotate the genomes of its participants, and to return individual genotype results of clinical significance to them (Biesecker et al. 2009). The death of this participant ("Participant 1") came to the attention of the research team when they attempted to contact him for clinical follow-up 2 years after his initial enrollment. Participant 1's partner informed the research team that some of his biological relatives were interested in receiving his individual genotype results. The research team was then faced with decisions about whether disclosure to family members was appropriate, how best to approach disclosure, and which results should be disclosed.

The questions of whether, how, and which genetic results should be disclosed to a proband's relatives are not novel.[1] However, these questions are complicated by the breadth of genetic analysis undertaken when using WES and WGS sequencing technologies. It is nearly inevitable that some actionable variations can be found for every research participant whose DNA is analyzed by these techniques. A typical WGS analysis generates approximately 4,000,000 sequence variations that differ from the current human reference sequence. A WES analysis typically yields 30,000–50,000 gene variants. While most variants are benign or of unknown consequence, some are associated with a significant increase in risk of disease for the proband and his/her relatives. The other novel aspect of employing WGS/WES is that it can uncover genetic variants that are not predictable on the basis of the proband's personal and family history of disease. WGS/WES analysis is thus unlike targeted or candidate gene research, where clinically actionable findings are comparatively infrequent and the nature of the potential findings is predictable.

[1]For example, Quaid et al. (2004) discuss the issue of disclosing genetic results to the relatives of deceased research participants, but this is within the context of target gene studies where the range of potential findings is restricted to one disease (e.g., early onset Alzeheimer disease). Offit et al. (2004) discuss the broader issue of a possible duty to warn a patient's family members about hereditary disease risks, but such a duty is unlikely to cover the full range of information uncovered in genomic analysis that relatives might have a legitimate interest in receiving.

Given the enormous variety and high frequency of clinically actionable findings in WES/WGS studies, the prospect of disclosing genomic results to deceased participants' relatives may seem prohibitively burdensome. However, we think that the methods employed to responsibly return WES/WGS findings to participants can in large part be translated to the disclosure of results to participants' relatives. We begin by summarizing the ClinSeq study and the case in question. We then present our ethical analysis in three parts. First, we explore a range of justifications for disclosing results to Participant 1's relatives. Second, we outline the methods the research team is using to disclose results in an ethically responsible fashion in this case. Finally, we argue that, at a minimum, a policy of "passive" disclosure to relatives is justified for those WES/WGS studies that already involve the disclosure of individual results to participants. Passive disclosure would involve disclosure of select results at relatives' request, without researchers actively offering to disclose these results.

Arguing for the possible disclosure of individual genetic results to deceased participants' relatives might seem surprising, given that there is ongoing debate about whether such results need always be reported to participants themselves.[2] Our general recommendations are restricted to those studies in which researchers are already committed to the responsible return of individual results to participants, as in the ClinSeq study. As we argue in the following, researchers who are able to address the concerns with returning results to participants should be well positioned to take the steps needed to responsibly disclose results to their relatives as well.

STUDY BACKGROUND

ClinSeq is an exploratory clinical genomics study that seeks to investigate most or all genes through WES or WGS and relate variants in genes to health and disease. In addition to this genotype–phenotype component of the study, another aim of the study is to return individual clinically relevant results from the sequencing to the participants in order to evaluate various modes of results returns, participants' reactions to these data, and the clinical utility of the data. Variants deemed to be clinically relevant could fall within a number of subcategories, including variants implicated in recessive conditions, variants that cause a disorder already present but undiagnosed or asymptomatic in the proband, variants that explain currently manifesting disease, and variants that predispose to later-onset conditions. ClinSeq participants decide whether or not to learn about these results each and every time one of these findings is uncovered for them. Disclosure only takes place if the participant is interested in that finding, and after the result is confirmed in a laboratory that has been certified for providing clinical test results.[3]

The exception to this general approach takes place if deleterious variants are identified that are implicated in conditions that may present a high risk of severely detrimental

[2]Overviews of the continuing debate over disclosure of individual results to participants can be found in Bredenoord et al. (2010), Fabsitz et al. (2010), and Ravitsky and Wilfond (2006). In their review of international and regional guidelines, Knoppers et al. (2006) suggest that there is an emerging consensus that there is a duty to disclose individual results to a research participant when there is clear evidence that the participant would benefit substantially, a long as the participant had not expressed his or her desire not to be informed. However, they find less agreement about an obligation to disclose results to affected family members.

consequences to the research participant, as in the case of malignant hyperthermia or Long QT syndrome, for example. In the case of these urgent findings, participants' preferences will *not* be assessed prior to verification and return of results. This policy is disclosed to participants in the informed consent process prior to enrollment.

A distinctive feature of ClinSeq is that it is a hypothesis-generating study, and variants of unknown clinical significance are key in the pursuit of novel genotype–phenotype relationships. These types of variants may lead to further clinical research evaluation of the proband for a specific phenotype, provided that he/she agrees to return for follow-up and consents to that clinical research study. Lastly, variants of uncertain clinical significance could be returned to participants in some circumstances—for example, if there is a reasonable suspicion that the variant is disease-causing and there are reasonable medical interventions available to mitigate the risk posed by the condition. This is unusual in genetics studies. However, evaluating participants' reactions and consequences of the return of such data are a research component of the study. The sequencing results are annotated in an ongoing, iterative manner in the ClinSeq study, potentially leading to multiple encounters between the research participant and the researchers for the disclosure of results deemed to be clinically significant. Participants may be contacted months or years after the initial date of enrollment.

CASE DESCRIPTION

Participant 1 was a 64-year-old male who enrolled in ClinSeq in July of 2008. His personal history of disease was significant for elevated cholesterol diagnosed in his early teens, hypertension in his 20s, and coronary artery disease in his 40s. He had quintuple bypass surgery in his 40s, and the placement of stents in his early 60s. During enrollment, he reported four living and genetically related adult children and a living younger sister. He was divorced from his first wife, and had been living with a long-term partner. Two years after his initial enrollment, a ClinSeq team member left a phone message for this participant to follow-up on a clinical, nongenetics result. The next day his partner of 12 years returned the call and informed the team that Participant 1 had passed away in his sleep about 2 months prior to the call. Participant 1 was alone at the time of his death, and no autopsy was performed.

In subsequent conversations with Participant 1's partner, she informed the research team that she had communicated with some family members about the ClinSeq study and that at least his sister and daughter seemed interested in receiving feedback from the study. The executor of Participant 1's estate, one of his sons, might also be interested in the information but was reportedly overwhelmed at that moment. After learning this information, the ClinSeq research team decided that the most appropriate course of action would be to obtain a consultation with the National Institutes of Health (NIH) Clinical Center's Bioethics

[3]These conversations are initiated by the study staff members, who phone the participant and give general information about the results. An example would be, "We have identified a DNA variant or change in you that suggests you have an elevated risk for a late onset disease for which there are preventative measures that may reduce this risk. While we cannot assure you that receiving such a result would be beneficial, it may be helpful to you and your doctors. Would you like to learn of such a result?" If they answer affirmatively, the research result is replicated in a clinical testing laboratory, a genetic test report is prepared, and the subject is invited in for medical and genetic counseling.

Consultation Service, given the novel challenges posed by whole-genome/whole-exome sequencing. In preparation for this consultation, the team confirmed with the research laboratory that Participant 1's sample had undergone whole-exome sequencing.[4]

After consultation with the ethics team and further discussion with Participant 1's partner, the research team made several attempts to contact Participant 1's son, who had been designated as the executor of his estate. The nature of the study was explained to him, including the types of genetics results that could be generated and the potential implications of such results to him and other relatives of his father. He was informed that, as the executor of the estate, he (or his appointed delegate) would be the point of contact in the family, responsible for liaising between his relatives and the research team. He expressed much interest in learning more about the study and receiving results from the sequencing of his father's sample. He confirmed that his sister was also interested in learning this information. Although he had not spoken with his brothers about the study, he mentioned that he would be willing to do so. A copy of the study consent form was sent to him along with additional information about the study. Once he reviewed these materials, the research team planned to communicate again by phone or in person to further discuss the study and the potential genotype results.

THE CASE FOR DISCLOSING RESULTS

In this section, we review the appropriateness of disclosing Participant 1's research results to his relatives in light of recent commentaries on a potential obligation to disclose incidental individual genetic research results. We conclude that certain kinds of results should be disclosed, given that family members had expressed a desire to receive the results and because those results were limited to those that would have a bearing on their health.[5]

Participant 1 did not leave specific instructions about the disposition of his research results after his death, nor was the matter addressed during the informed consent process, as the possibility of postmortem disclosure of results to relatives had not been foreseen. At the time of enrollment, the participant indicated that his reasons for participating were to understand his condition (heart disease) and a general desire to help advance research. Absent specific directions from the research participant, the literature suggests that there is a presumption in favor of releasing genetic test results that are relevant to the health of the proband's relatives and, more generally, to respect relatives' wishes about how the proband's information should be handled (Annas et al. 1995, sec. 133;Wertz et al. 2003, 85).[6]

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[4]Had his sample *not* yet been sequenced, the research team would have kept the sample in the sequencing pipeline since that would have been consistent with the scientific aims of the study.

[5]Note that we are not discussing the *legality* of the disclosure; while releasing the participant's research results to his family members was legally permitted, legal restrictions on disclosure will vary depending on the context of the research. Deceased participants are not covered by the Common Rule for human subjects protection (45 CFR 46). Participant 1's results were not covered by the HIPAA, as the NIH is not a "covered entity." An NIH research participant's information is covered instead by the Privacy Act 5 USC s. 552, according to which release of Participant 1's research results is permitted upon written request of a legally authorized representative (in this case, Participant 1's executor).

[6]For example, see Wertz et al. (2003, 85): "DNA should not be considered the 'private property' of one individual … It should be possible to inform others who share part of an individual's DNA, namely biological relatives, about their own health risks and also to allow them access to the DNA which is shared property." The Annas et al. (1995) model Genetic Privacy Act includes an explicit exception for genetic information that would benefit the relatives of a deceased proband (Section 133). For an argument in favor of relatives' access in a specific context, see Lucassen et al. (2004).

The primary consideration in favor of disclosing results to Participant 1's relatives is beneficence, since the analysis of the participant's genome may yield findings that would enable his relatives to make better decisions regarding their own health. His relatives would otherwise probably not receive such information, given the novelty of whole-genome medical sequencing. The ClinSeq research team may thus be able to confer unique benefits to Participant 1's relatives. Still, among the many opportunities one has to benefit others, it is often difficult to distinguish those cases where beneficence is morally required (i.e., a duty) from those where beneficence is morally commendable but not required. We do not argue that disclosing results to Participant 1's relatives is morally required. Rather, we hold that the possibility of benefiting his relatives provides the ClinSeq team with a reasonable justification to disclose results that is not undermined by the common objections to disclosure to relatives.

There are three conditions that are commonly cited as reasons for *not* disclosing such information to the family members of a deceased participant (Sexton and Metcalf 2008)[7]: if there is good reason to believe that the decedent would have objected to the release of information, if the wishes of the potential recipient of the information are unknown, or if researchers lack the analytic or clinical resources to responsibly disclose the findings. While we do not think that the presence of one of these conditions should necessarily prevent the disclosure of results to relatives—for example, if there are findings of urgent importance—we forego discussion of the validity of these conditions here, as none of the conditions apply to the potential disclosure of results to Participant 1's family.

First, there is no good reason to believe that Participant 1 would have objected to the disclosure of his research results. To the contrary, the team was aware that this participant had openly talked about his participation in ClinSeq with his family. In addition, a qualitative survey of 322 ClinSeq participants found that one of the main motivations for individuals to enroll in the study is to gain information that would be of use to family members, particularly their children (Facio et al. 2011). Moreover, only results that were clinically useful for his relatives would be disclosed, further reducing the chance that researchers would be sharing information Participant 1 would have wanted to remain confidential. Second, the family members would be receiving results at their own request, vitiating the concern that researchers would be sharing information that the recipients did not wish to receive. Finally, the research team possesses the analytic resources to focus on clinically valid findings, and to communicate those findings through genetic counseling that addresses both the medical educational and counseling needs of the family.

The research team has since encountered two other cases in which ClinSeq participants have passed away. These additional cases highlight how several factors that are relevant to disclosing genetic results after a participant's death can (and will) vary: the existence and relatedness of biological relatives, the interest that family members have in receiving results, and the extent to which the participant's sample has been analyzed.

[7]An additional requirement—that the disclosure *policy* be publicized—is discussed in Savulescu and Skene (2000). See also Quaid et al. (2004, 352–353) for a summary of opinions on the disclosure of genetic information from deceased participants.

The death of Participant 2 was communicated to the team by one of his colleagues, who was also a study participant. Unlike Participant 1, Participant 2's sample had not been sequenced when the research team learned of his death.[8] Participant 2 was an only child and did not have any biological children. Although he has living aunts and cousins on the paternal side of his family, at the time of enrollment he reported that he did not know any information about these relatives. His wife reported that she was curious about the genetic variants that would be found for her husband, particularly if they explained his history of early-onset coronary artery disease. She understands that this information has no direct bearing on her health.

The death of Participant 3 came to the attention of researchers when the research team went back to the NIH clinical center database to look at laboratory values and found a notation about his death. The wife was the executor of the estate and, as such, was the person who would be making decisions with regard to his genetic results going back to biological relatives, including their two adult daughters. However, she felt that her daughters would not be interested in learning about disease-causing variants found in their father's sample based on their previous attitude toward testing for a gene that could be of importance to them based on their paternal family history of disease. Although she was hesitant to approach them, she did plan on explaining the nature of the study to them and the possibility of learning genetic results that could be of potential medical relevance to them.

The argument for disclosing genetic results is thus clearest in the case of Participant 1. His family included first-degree biological relatives, unlike that of Participant 2, thus providing medical relevance as genomic analysis will likely include findings that are clinically actionable. In addition, Participant 1's sample had already been sequenced and partly analyzed. Finally, Participant 1's relatives were interested in learning about such findings, unlike the relatives of Participant 3. In the remaining sections, we turn our attention to how results will be disclosed to Participant 1's family, and the implications for other WGS/WES study participants.

The three cases already described represent just a few of the many permutations the research team could expect to encounter, given the number of individuals enrolled in the study (currently greater than 900) and the unique attributes of each family. In addition, WES/WGS research has the promise of uncovering an enormous variety of individual results that are clinically actionable, many of which we cannot now predict. Again, the implication of the breadth of WES/WGS analysis is that each participant is highly likely to have clinically actionable variants. In our view, it is thus inadvisable to set rigid conditions for disclosure in advance. Instead, the research team is following a flexible process that largely mirrors that used for the return of results to living ClinSeq probands, which we describe in the next section.

[8]Since sequencing his sample postmortem is consistent with one of the main aims of the study—to elucidate the role of gene variants in health and disease—the team decided to keep his sample in the sequencing pipeline, independent of any interest that his wife has in the results of the analysis.

A METHOD FOR DISCLOSING RESULTS

Once we had decided that disclosing results to Participant 1's family was appropriate, three main questions followed: Which results should be disclosed? To whom should results be disclosed? And how should they be disclosed?

In order to determine which results to disclose, it is important to ascertain the prospect of benefit for disclosing various sorts of results. However, given the broad range of possible findings in WES/WGS—from dominant susceptibility genes with effective prophylaxis or treatment (e.g., *BRCA2*) to recessive genes relevant to reproductive decision making (e.g., *CFTR*)—a precise estimate of the likely benefit to the family members is difficult to determine. Again, this is dramatically different from traditional candidate gene research, where the nature of the possible results can be anticipated with some precision. Given the broad variety of possible results, it is important to restrict disclosure to those variants whose clinical significance is well established.

The research team considers a variant clinically significant if there is evidence that the variant is linked to a significant harm *and* there are measures that one can take to prevent or treat the potential harm. For example, the risk of colon cancer can be markedly reduced by early and frequent colonoscopy in some heritable colon cancer syndromes, such as hereditary non-polyposis colorectal cancer syndrome (Jarvinen et al. 2000). The relatives could determine, through independent testing, whether they also possess the variant and take preventative measures in response. By contrast, knowledge that one possesses the variant linked to Huntington's disease would not improve treatment or prevention, and would not be a candidate for disclosure to participants' relatives. This approach differs from what is disclosed to participants; although the research team may disclose variants of uncertain clinical significance to study participants, they will not disclose such variants to family members. While relatives may be interested in learning about such variants, disclosing such results is not supported by the beneficence rationale that provides the foundation for disclosing results to them.

Deciding *to whom* to disclose results involves balancing logistical, ethical, and clinical considerations. The research team has decided to designate a single member of the family—the executor of the decedent's estate—to act as the decision maker and recipient of the participant's research results on behalf of the surviving family. If the executor is not a family member, the research team will discuss with him/her whether a relative could be appointed as the decision maker, and which relative would be best suited for this role. Logistically, picking one person to serve as decision maker minimizes the administrative burdens involved with disclosing results. Ethically, beginning with the presumption that the executor will receive the results makes sense given that he or she is already entrusted with the disposition of the decedent's affairs.

However, designating a single relative to serve in this role might diminish the clinical utility of disclosing results, if the results were not subsequently communicated to other family members. Though data on these phenomena are limited, they support the commonsense belief that family members sometimes neglect to communicate important health-related

findings to relatives who are at least as likely to be affected as they are.[9] Note that this is a problem the research team encounters with ClinSeq participants themselves, given that the ClinSeq team discloses results to the probands and relies on him/her to disseminate the information to other at-risk relatives. In the case of Participant 1, the plan is to communicate results to the executor of the estate and encourage him to disseminate the information to the rest of his family. To maximize his ability to convey the information to his relatives, the study's genetic counselor has initiated conversations about the communication patterns within the family, the willingness on the part of the executor to reach out to relatives with whom he does not have a close relationship, and the manner in which he would approach them to introduce this sensitive topic.[10]

The process for disclosure will be the same followed for ClinSeq probands to the extent that the executor of the estate will be contacted once research findings deemed to be clinically significant are uncovered, and he will be asked to make a decision on behalf of his family members about whether the research team should confirm the results in a clinically certified laboratory and return that information to him. He will then be asked to come to the NIH for a face-to-face consultation with a geneticist and a genetic counselor. If clinically significant variants are found, he will be advised that he and his relatives should undergo testing for those variants through a clinical molecular testing laboratory. The researchers will *not* be involved in the testing of the relatives, nor in any treatment or preventative measures that might follow if relatives confirm that they possess the variants as well.

The sequencing data for the deceased participant will continue to be annotated on an ongoing, iterative manner; consequently, there could be multiple encounters between the executor and the researchers for the disclosure of results deemed to be clinically significant, and the executor could be contacted months or years after the initial date of his father's enrollment (although not all of these potential future communications will need to occur in person).

DISCUSSION: PLANNING FOR FUTURE CASES

Researchers deploying WES/WGS technologies should be aware of the possibility that family members may want to receive the results of deceased research participants. Thus far we have presented an approach for disclosing such results once such a request is received. The question we turn to now is: What should researchers do in anticipation of such requests? We first outline the active disclosure plan for the ClinSeq study, with particular attention to how participants will be informed of the possibility of postmortem disclosure to their relatives. We then argue that, at a minimum, WES/WGS researchers who plan to return

[9]In their review of the 26 studies on familial communication of genetic information, Gaff et al. (2007) find that the processes by which such information is disseminated within families remains poorly understood. See also Ormondroyd (2008), a small study of how information about *BRCA2* mutations was (and, more importantly, was not) communicated among family members. The study outlines a common"top-down" approach where older family members are responsible for informing younger family members.

[10]For example, the executor stated that although he is in communication with his sister and knows that she is interested in the information the research team can provide, he had not had a discussion about this with his other siblings. The genetic counselor followed this by asking: "Do you think your brothers would be interested in receiving this information? Would you be willing to speak with your brothers about your father's participation in the study? And, would you be willing to relay to them the possibility that you and your siblings are in a position to learn about genetic results for your father that could have implications to your own health? How do you believe they would react to such a conversation?"

individual results to participants should also plan on the *passive* disclosure of some results to the relatives of deceased participants; that is, they should plan on disclosing some results *if* the relatives of deceased participants request them, though they need not actively offer to disclose that information. This is because the relatively small burden of a passive disclosure policy does not provide a strong reason to cut relatives off from the potential benefits of receiving genetic results.

In future cases, the ClinSeq research team plans to follow the same procedure that it is following with the families of Participants 1, 2, and 3, once it learns that a proband is deceased. This includes making a reasonable effort to engage the executor of the estate, or in the absence of an executor, the next of kin to determine whether the family has an interest in receiving individual genotype results deemed to be clinically or medically significant. While other family members may be interested in obtaining results and may feel that they are better suited to make decisions about the return of results, communicating with the executor and asking him/her to be a liaison to other family members offers a balance between making the results available to at-risk relatives, respecting the wishes of the participant, and mitigating the burden on researchers. In addition, the executor can delegate the responsibility of acting as the point of contact to another family member, and may be encouraged to do so if another relative is in a better position to take on that responsibility.

Informing current and prospective participants of the possibility of postmortem disclosure of results to relatives is an important part of this disclosure procedure. After the research team encountered these three cases, they made the decision to inform other ClinSeq participants of this process for communicating with the executor through the study newsletter, which is sent to all participants biannually. Additionally, the newsletter reminded participants to (1) discuss their involvement in the study with their family members and (2) encourage their family members to contact the research team in the event the proband passes away. Communicating this disclosure process to participants in advance allows current participants to retain a large measure of control over their results by choosing whether to discuss their participation with their families, and it places the responsibility of first contact about a participant's death on the relatives, given that the research team may not be aware of such an event unless it is communicated to them directly.

The research team did not choose to alter the ClinSeq consent form so as to give future participants the option of shielding their information from family members. The primary reason against giving this option is the belief that a research participant does not have the ethical authority to preemptively prevent relatives from obtaining information that could be of clinical benefit to them after his or her death. In our estimation, providing participants with this option during the consent process would be making a promise that could be unethical to keep. Discussion of privacy protections is a central part of the study's consent process, and participants are informed that postmortem disclosure of results to relatives is possible, and, more generally, that there are exceptional circumstances under which their research results might be shared with others.

While we encourage active disclosure to relatives in studies where the resources for making such disclosures are already in place, we stop short of claiming that all future WES/WGS

studies should include provisions for such disclosure. From a societal perspective, there are at least two sets of questions that would have to be settled in order to determine whether to support or reject such a broad change in the genomics research environment.[11] The first set pertains to the distinction between research and care. For example, would the wide adoption of an active disclosure policy hamper medical research by contributing to an undesirable confusion between research and therapy, or would it promote the research enterprise by fostering greater trust between research participants and genetics researchers? The second set concerns the distributive consequences of widespread active disclosure to relatives. For example, are the benefits to relatives great enough to warrant the commitment of resources that would be needed to fund a general policy of active disclosure? Would it be just to implement a policy that gives the relatives of research participants early access to the benefits of WES/WGS screening? Given these open questions, and the lack of consensus about how best to manage incidental findings more generally, we think that it is prudent to take a cautious but forward-looking approach.

At a minimum, a policy of *passive* disclosure to relatives is sensible for WES/WGS studies that involve disclosing individual results to participants. The qualification is an important one. WES/WGS studies vary in their design, and it would be difficult to justify a policy disclosing results to relatives when results are not being returned to participants. However, when a study already involves disclosing individual results to participants, we believe that researchers ought to passively disclose clinically significant results to relatives (and for the subset of urgent findings noted in the previous section, active disclosure is appropriate).

A policy of passive disclosure to deceased participants' relatives steers clear of familiar concerns with disclosing individual genetic results more generally. Consider the five major concerns that motivate restrictive policies on disclosure to research participants: that disclosing individual results promotes the therapeutic misconception, it rests on a mistaken interpretation of autonomy, it is not feasible, it has harmful consequences, and it poses an untenable burden on the research infrastructure (Bredenoord et al. 2010).

We believe that the first two concerns are not particularly relevant to the question of disclosing results to relatives. The therapeutic misconception—mistaking clinical research for individualized care—is morally troubling when it undermines a person's ability to provide legitimate informed consent to research participation. As the relatives are not themselves participants in the study, disclosing results to them does not threaten to undermine the permissibility of the researchers' interaction with them. Indeed, since the researchers are interacting with the relatives for the relatives' benefit, and not for the purpose of research, the relatives would not be mistaken to think that the researchers are acting as clinicians rather than researchers in their interactions with them. There is also little reason to worry that disclosure to relatives rests on a mistaken interpretation of autonomy, since the rationale for disclosing results to relatives is beneficence and not respect for their autonomy.

[11]We thank the anonymous reviewer who brought these questions to our attention.

The final three concerns—feasibility, harm, and burdensomeness—*are* relevant to the disclosure of results to relatives. However, any study that answers these concerns with respect to participants should also be able to answer them with respect to deceased participants' relatives. First, since the studies under discussion already involve the return of results to participants, the requisite analytical and clinical capabilities for responsibly disclosing individual genetic findings are presumably already in place. This suggests that disclosing results is feasible and that the potential for harm due to misinterpretation of results by researchers or participants' relatives is minimized, due to the safeguards put in place for return of results to participants. Second, a passive disclosure policy—researchers will not routinely disclose results to relatives, family members must make the request themselves—should help to minimize the additional burden placed on researchers. Among the subset of relatives of deceased participants that contact researchers, many may not be interested in receiving results (like the relatives of Participant 3). Thus, we think that these concerns do not rule out disclosing results to family members in studies like ClinSeq, which involve disclosure of results to participants.

While we believe that a passive disclosure policy to relatives is justified, we recognize that several of the reasons that support a duty to disclose genetic results to participants do not apply to passively disclosing results to their relatives. For example, researchers have no obvious duty of reciprocity to participants' relatives, nor is there typically a special relationship formed between researchers and relatives that enjoins the disclosure of individual research results. Instead, the primary reason for implementing a passive disclosure policy is beneficence: making the benefits of WES/WGS available to participants' relatives. Participant 2's case, where there are no surviving first-degree relatives, may show the limits of a beneficence rationale for disclosing results. The participant's wife has an interest in learning about her deceased husband's results, so as to better understand his coronary disease. While disclosing Participant 2's results may bring his wife a personal benefit, it differs significantly from the potential health benefits to the relatives of Participant 1. The justification for disclosing findings that may be clinically relevant to Participant 1's relatives is congruent with a central reason for disclosing results to participants themselves: so as to enable better health/medical decision-making. Since disclosing Participant 2's results does not confer a significant health benefit, it is less clear that there is a compelling reason to disclose in that case.

One can imagine other variations that would further complicate the decision to disclose results to deceased participants' relatives—for example, if the participant expressed a desire to keep his (or her) results from his family, or if an executor (and presumptive recipient of results) disagreed with other relatives about which results to receive. Rather than attempting to draw a line that sorts all possible disclosures and cases, we recommend the following: At a minimum, researchers should enact a passive disclosure policy so as to enable relatives to obtain results that are of potentially significant medical benefit. It is extremely difficult to draw a sharp line dividing cases where beneficence is a duty from those where beneficence goes beyond the obligations of a clinical researcher. However, given the possibility of significant medical benefits to family members and the minimal burden of a passive return policy, we think it would be unreasonable for researchers who plan to disclose individual

results to participants not to plan on the passive disclosure of results to participants' relatives —just as it would have been unreasonable for ClinSeq researchers to simply deny Participant 1's family's request.

REFERENCES

Annas, G.; Glantz, L.; Roche, P. The Genetic Privacy Act and commentary. Boston: Health Law Department, Boston University School of Public Health; 1995.

Biesecker L, Mullikin JC, Facio FM, et al. The ClinSeq project: Piloting large-scale genome sequencing for research in genomic medicine. Genome Research. 2009; 19:1665–1674. [PubMed: 19602640]

Bredenoord AL, Kroes HY, Cuppen E, Parker M, van Delden JJM. Disclosure of individual genetic data to research participants: the debate reconsidered. Trends in Genetics. 2010; 27(2):41–47. [PubMed: 21190750]

Eng S, Nickerson DA, Bamshad MJ, Shendure J. Massively parallel sequencing and rare disease. Human Molecular Genetics. 2010; 19(R2):R119–R124. [PubMed: 20846941]

Fabsitz R, McGuire A, Sharp RR, et al. Ethical and practical guidelines for reporting genetic research results to study participants. Circulation Cardiovascular Genetics. 2010; 3(6):574–580. [PubMed: 21156933]

Facio FM, Brooks S, Loewenstein J, Green S, Biesecker LG, Biesecker BB. Motivators for participation in a whole-genome sequencing study: implications for translational genomics research. European Journal of Human Genetics. 2011 [Epub ahead of print].

Gaff CL, Clarke AJ, Atkinson P, et al. Process and outcome in communication of genetic information within families: A systematic review. European Journal of Human Genetics. 2007; 15:999–1011. [PubMed: 17609674]

Jarvinen HJ, Aarnio M, Mustonen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology. 2000; 118:829–834. [PubMed: 10784581]

Knoppers BM, Joly Y, Simard J, Durocher F. The emergence of an ethical duty to disclose genetic research results: International perspectives. European Journal of Human Genetics. 2006; 14(11): 1170–1178. [PubMed: 16868560]

Lucassen A, Parker M, Wheeler R. Role of next of kin in accessing health records of deceased relatives. British Medical Journal. 2004; 328(17):952–953. [PubMed: 15087350]

Offit K, Groeger E, Turner S, Wadsworth EA, Weiser MA. The3duty to warn" a patient's family members about hereditary disease risks. Journal of the American Medical Association. 2004; 292(12):1469–1473. [PubMed: 15383518]

Ormondroyd E, Moynihan C, Ardern-Jones A, Eeles R, Foster C, Davolls S, Watson M. Communicating genetics research results to families: Problems arising when the patient participant is deceased. Psychooncology. 2008; 17(8):804–811. [PubMed: 18688787]

Quaid K, Jessup N, Meslin E. Disclosure of genetic information obtained through research. Genetic Testing. 2004; 8(4):347–355. [PubMed: 15727261]

Ravitsky V, Wilfond B. Disclosing individual genetic results to research participants. American Journal of Bioethics. 2006; 6(6):8–17. [PubMed: 17085395]

Savulescu J, Skene L. Who has the right to access medical information from a deceased person? Ethical and legal perspectives. Journal of Law, Medicine and Ethics. 2000; 8:81–87.

Sexton A, Metcalfe S. Disclosing genetic research results after death of pediatric patients. Journal of the American Medical Association. 2008; 300(14):1693–1695. [PubMed: 18840844]

Wertz, D.; Fletcher, J.; Berg, K. Review of ethical issues in medical genetics. Geneva: World Health Organization; 2003.