Models of Consent to Return of Incidental Findings in Genomic Research

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Investigators who conduct whole genome sequencing presumably should inform subjects that the study could generate findings that lie beyond the primary aims of the research but might be very important to the subject. But how should they tell them about that possibility, and how should the findings be relayed?

Genomic research—including whole genome sequencing and whole exome sequencing—has a growing presence in contemporary biomedical investigation. The capacity of sequencing techniques to generate results that go beyond the primary aims of the research—historically referred to as "incidental findings"[1]—has generated considerable discussion as to how this information should be handled—that is, whether incidental results should be returned and, if so, which ones.[2] We previously reported strong support among genomic researchers for the return of medically actionable data and substantial support for offering participants findings related to reproductive choices, pharmacogenetics, and highly penetrant disorders without available clinical interventions.[3] Others have reported comparable results,[4] and a number of expert groups have taken similar positions.[5] Participants in genetic research are reportedly extremely interested in receiving most classes of genetic findings.[6]

Important questions remain to be answered about how incidental findings may be identified and returned to research participants. Some genomic studies involve the interrogation of large parts of the genome, making identification of incidental findings quite likely. However, in many sequencing studies, data can be filtered selectively, permitting investigators to control the extent to which incidental findings are likely to be identified.[7] Whether genomic researchers will ultimately be deemed to have an obligation to search for certain categories of incidental findings and how extensive those categories may be remain undetermined. Similarly uncertain is the extent to which participants will be able to choose

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Investigators will face considerable challenges in framing meaningful disclosures for research participants.

which types of findings they will receive, although making such options available has been widely endorsed.[8] In studies in which the identification of incidental findings is probable and investigators undertake to make them available to participants, questions about how best to inform participants and obtain their consent inevitably arise.[8]

Federal regulations governing most human subjects research in the United States require the disclosure of "the procedures to be followed" in the research as part of the informed consent process.[10] It seems reasonable to assume—and indeed, many commentators have concluded[11]—that genomic investigators will be expected to inform participants about, among other procedures, the prospect that incidental findings will become available and the mechanisms for dealing with them. Moreover, the regulations mandate disclosure of "reasonably foreseeable risks" and "any benefits to the subject or to others which may reasonably be expected";[12] to the extent that the availability of incidental findings may evoke both risks and benefits for participants, they will need to be revealed as well.[13] Other potentially relevant sections of the regulations relate to disclosure of "the extent, if any, to which confidentiality of records identifying the subject will be maintained" and "additional costs to the subject that may result from participation."[14] These are issues that genomic investigators and institutional review boards will need to consider in drafting and reviewing informed consent procedures for genomic research.

Challenges to Obtaining Informed Consent

On its face, obtaining informed consent regarding the possible discovery of incidental findings—in compliance with the federal regulations as well as the widely recognized ethical duties on which the regulations are based—presents a number of challenges. Because in many studies the range of potential results will be so great as to preclude listing specific possibilities, broader groupings (often referred to as "bins"[15]) may need to be used. If participants are given the option of consenting to the return of data in some but not all of these bins, they will need to be told about and to select among types of conditions by probability of developing the disease, severity of disorder, availability and effectiveness of interventions, reproductive implications, or other dimensions. In addition, given that investigators will, when prospectively discussing the return of incidental results with participants, know neither the likely findings nor their potential implications, the discussion of possible risks and benefits will lack specificity and may necessarily be speculative. It will reflect the unknowns inherent in this process. Insofar as genomic data often carry implications for family members in addition to participants, these too may need to be described to participants. Investigators, most of whom will not have dealt with these issues before, will thus face considerable challenges in framing meaningful disclosures for research participants.

To help genomic investigators in this task, we undertook to identify the elements that should be included in the informed consent process related to incidental findings.[16] We did this by surveying a large number of genomic researchers (n = 241) and by conducting in-depth interviews with a smaller number of researchers (n = 28) and genomic research participants (n = 20). The value of this approach is that it directs attention to the relevant sources: common law standards for informed consent in clinical care look either to the usual practice of physicians (a "professional standard") or to the informational needs of patients (a "lay standard') to determine the required scope of disclosure.[17] Although consent in research settings operates with an overlay of regulatory requirements, ascertaining the views of investigators and participants remains meaningful. In our survey and interviews, we presented our respondents with options regarding the types of information about incidental findings that might be disclosed to research participants and asked whether they thought each item should be included in informed consent disclosures. Options were taken from an exhaustive literature review on incidental findings. We also queried respondents on what other pieces of information should be included.

Our findings about the risks and benefits of returning incidental findings showed that a majority of the researchers surveyed endorsed discussion of a wide range of risks (for example, negative psychological responses or false negative or false positive findings) and benefits (identification of treatable disorders or enhanced life-planning ability). The genomic research participants interviewed were even more strongly in favor of disclosure. Respondents were also just as strongly in favor of discussing

Table 1.
Four Models of Consent to Return of Incidental Findings

	Potential advantages	*Potential disadvantages*
Traditional consent: Participants receive all information about incidental findings prior to deciding whether to participate.	• The process is familiar to researchers. • Participants maintain choice about receipt of incidental findings.	• Explaining the information adds to an already lengthy and complex process. • Participants' preferences may change after initial consent.
Staged consent: Participants receive information about incidental findings later, as they arise.	• Less time is spent discussing incidental findings during initial consent. • Participants maintain choice about receipt of incidental findings. • Participants can consider changing circumstances when deciding whether to receive incidental findings. • Participants can receive more detailed and specific information when deciding whether to receive findings.	• Following up and recontacting participants for consent could be costly and burdensome. • Participants decide whether to enroll in study without receiving full information about potential incidental findings. • Depending on the procedure, recontacting the participant can itself reveal unwanted information.
Mandatory return: Participants agree during initial consent to receive specified incidental findings.	• Consent at enrollment is simpler. • Researchers' obligations to return incidental findings are clearly defined. • Participants maintain choice about whether to participate in the study.	• Participants' choices about receipt of incidental findings are restricted. • Lack of participant choice may be a disincentive to enroll in the research. • Following up and recontacting participants could be costly and burdensome for researchers.
Outsourcing: Participants receive all raw data and may hire an outside service to interpret data and learn of incidental findings.	• Researchers save time and costs associated with return of incidental findings. • Participant is spared immediate task of deciding which findings to receive. • Researchers' obligations are simplified.	• Interpretive services are not yet widely available. • Interpretive services may be costly and limited to wealthy participants. • Participants who do not hire an interpretive service may not learn of medically significant data.

information about the possible impact of incidental findings on family members; protections for the confidentiality of the findings; procedures related to the return of incidental data should participants become impaired or deceased; whether incidental findings generated in subsequent research or as a result of advances in interpretation would be offered to participants; and the circumstances, if any, in which participants' choices about return of incidental findings could be overridden. Additional categories of information suggested for discussion included the possibility that incest or misattributed paternity would be detected and the extent to which the data would be shared with other researchers.

Based on the responses of investigators and research participants to our survey and interviews, and even taking into account a potential tendency to endorse whatever options were presented, it was clear that both parties expect a large amount of information about possible return of incidental findings to be exchanged. In the in-depth interviews, though, researchers and participants alike expressed concern over the ability of participants to attend to and comprehend such extensive disclosures, especially in the context of additional disclosures regarding the study for which sequencing was to be performed. In addition, when researchers were asked how much time they were willing to devote to informed consent regarding incidental findings, 44 percent said they would spend fifteen

minutes or less, while 77 percent said they would not exceed thirty minutes. Thus, there seemed to be a striking disjunction between the amount of information to be disclosed and the time investigators thought they could make available to disclose it.

Based on these findings and as explained further below, it seems clear to us that routine approaches to informed consent are not likely to be effective in genomic research in which the prospect of incidental findings exists. Ensuring that participants' decisions are informed and meaningful will require innovative approaches to dealing with the consent issue.

Models of Informed Consent

Drawing on our review of the literature on return of incidental findings and the responses of the researchers and participants we interviewed, we have identified four prototypical models of a consent process for return of incidental findings. The first of these reflects the traditional approach to obtaining consent, while the other three embody creative alternatives. We describe the advantages and disadvantages of each below. However, we recognize that there are likely to be multiple permutations of these models, including hybrid approaches that blur the boundaries between them, and that other models may grow out of the field's evolving experience with genomic research. Another alternative, of course, would be not to return incidental findings at all, obviating the need for any of these models.

Model 1: *Obtain consent to return of incidental findings at the time of enrollment into the genomic research study (the "traditional consent" model)*

On its face, the most straightforward model of consent to return incidental findings is to incorporate discussion of the issue into consent to participation in the underlying research. That is, a portion of the informed co_nsent form and consent discussion—primarily focused on soliciting the potential subject's agreement to enter a study involving genome sequencing—would be set aside for discussion of incidental findings. This discussion would cover the nature and likelihood of incidental findings; the categories of findings that may be detected; the options available to participants for returning some, all, or none of the findings; the benefits and risks associated with return of incidental findings; and associated information, such as confidentiality of the data, implications for family members, and how data will be handled in the event of a participant's death or disability. After the discussion, participants would be asked to choose which, if any, results they would want to receive from those categories that the study has decided to make available to them (for example, evidence of serious conditions that are preventable or treatable, of serious conditions that are not medically actionable but may affect life planning, of carrier status, or of pharmacogenetic status). The decision would be embodied in the consent form by means of participants' signatures or initials.

The advantages of this model are considerable. Consent to all aspects of a genomic research study would be obtained up front so that participants would be aware of the major risks, benefits, and related information that might affect their decisions about entering the study. To the extent that the prospect of generating certain types of incidental findings might lead participants to decline participation, for example, because of concerns about potential discriminatory impact should predispositions for serious disorders be identified, participants would have the opportunity to make that choice at the outset on an informed basis. Conversely, insofar as the possibility of receiving incidental findings would be an incentive for participation, the dimensions of the return of potential findings would be clear. Moreover, from the perspective of the research team, this discussion would take place as part of a familiar and clearly defined process that reflects the usual flow of clinical research—that is, consent to all study procedures would be obtained prior to participants' entry into a study.

However, there are also substantial disadvantages to incorporating discussions of incidental findings into the usual consent process. As noted above, investigators and participants anticipate that a substantial amount of information will need to be communicated to facilitate informed decisions regarding return of incidental findings—though investigators appear to be reluctant to set aside more than fifteen to thirty minutes for the purpose. Inevitably, a consent process that is already lengthy and complicated[18] will be extended even further, and even so, the time allocated may be too limited to convey adequately the additional complexities involved. Similar problems may be evident with informed consent forms for genomic research, which in our experience already typically range from ten to twenty single-spaced pages, depending on the complexity of the study, with reading levels well in excess of the usual recommendation (that is, not to exceed an eighth-grade level). A good deal of evidence suggests that potential research participants

A majority of the researchers and genomic research participants favored disclosure of incidental findings.

currently receive more, and more complex, information than they can reasonably assimilate and use in their decisions.[19] Adding more information into the mix seems a recipe for poorly informed decision-making about return of incidental findings and may, by virtue of the confusion it would engender, discourage some potential subjects from participating in the underlying research.

To be sure, some of these problems could be mitigated by providing participants with information in advance of when their informed consent would be obtained or by having multiple interactions with them over a period of time (perhaps one to two weeks). Written materials could be supplemented with access to online video or multimedia resources, allowing participants who so desire to explore the issue in depth prior to the final consent transaction with the researcher. Guidelines for ensuring the quality of such "decision aids" have recently been developed.[20] However, the underlying problem would remain: potential participants would still be receiving a great deal of information about both the study and possible incidental findings over a relatively short interval, and they would be asked to make a variety of decisions at a single point in time.

Model 2: *Obtain consent in stages, with brief mention of incidental findings at the time of initial consent but with more detailed consent obtained if and when reportable results are found (a "staged consent" model)*

One alternative to obtaining consent to return of incidental findings at the time of enrollment would be to defer the process of decision-making about returning them until later in the process. One could, for example, initially obtain consent for participation in a genomic sequencing study and, at some later point, have a second conversation specifically to help people understand the types of incidental findings that may arise and to make choices about which of the available data they would like to receive. Approaches like this have been used in nongenomic pediatric cancer studies to allow sequential consideration of the decisions that need to be made.[21] Alternatively, one could postpone the process regarding decisions about receipt of incidental findings until it was clear whether there would be such findings for a given participant. The likelihood of such findings will vary across studies, depending on the scope of reportable results defined in each protocol. When consent to participation was obtained, participants would be told that incidental findings might be detected in the relevant categories and that they would be given an opportunity, if such results were found, to learn more about them and decide whether to receive them. When study consent was initially obtained, the possibility of incidental findings would be described in general terms, along with the system for notification. If incidental findings were discovered, participants could be approached again, told that some findings existed, and engaged in a discussion of the risks and benefits of learning about the results.

One example of this latter variation of the model is the "informed cohort" approach proposed by Isaac Kohane and colleagues,[22] which has been adopted by the Coriell Personalized Medicine Collaborative.[23] Although not focused specifically on incidental findings, the project makes sequencing findings about potentially actionable conditions available to research participants. When a result becomes available, participants are notified by an email that includes "generalities about the condition" to which the finding relates.[24] Prior to deciding whether to view the result in their individualized web-based portal, participants can pull up online educational materials about the condition in question and gain access to genetic counselors and trained pharmacists for additional information. Participants who decline to receive a particular finding can return and do so at any later point,[25] approximating what has been described as the "self-guided management" of sequencing results.[26] A similar model has been described for the My46 genomic sequencing project at the University of Washington and for direct-to-consumer genome testing.[27] (A variant of this approach was adopted by The Gene Partnership at Children's Hospital in Boston, whose participants can indicate in advance the general categories of findings they would like to receive and are contacted only with regard to those results.[28])

Staged consent of this sort enhances the efficiency of the initial consent process by allowing participants to focus on the core question of whether to join the genome sequencing study, knowing that they can defer deciding about the issues related to the return of incidental findings. Additional efficiencies can be obtained by postponing the discussion of options related to return of incidental findings until such findings are detected, entirely eliminating the need for such discussions with participants for whom no returnable incidental findings will be found. Participants' ultimate decisions may be better informed with this approach, since detailed information specific to the findings in question can be provided when those decisions need to be made. At that point, participants may be more motivated to pay attention to the information and focus on the decision, knowing that something has been discovered and that a choice must be made. Decisions can also be based on their current personal, medical, and familial status, any of which may have changed since the time of enrollment.

Nevertheless, the disadvantages associated with this model are real. Participants may be consenting to the sequencing study without fully appreciating the subsequent choices they will face—which arguably may undercut the meaningfulness of their consent. For this reason, some IRBs and investigators may be uncomfortable with this approach. In addition, when consent is deferred until findings are in hand, the very act of

None of the possible models for informed consent to return of incidental findings in genomic research is ideal.

contacting the participants, whether by email or in person, will suggest or reveal information that participants may not want to have. Communicating, for example, that the study has detected an incidental finding regarding a propensity for heart disease may, in a real sense, preempt a participant's decision as to whether he or she wants to know about cardiac risks. For people who may experience distress and anxiety at the prospect of future illness, even if they decline further information at that point, the harm has already been done. Indeed, insofar as participants choose not to learn more about the finding, they may actually exaggerate the degree of risk or inability to affect the outcome, compounding the negative impact. Although this problem can be mitigated by providing increasingly specific information in sequential communications (for example, indicating first that a finding is available and providing additional information only if a person wants to know more), it cannot be entirely eliminated. Finally, from a practical perspective, the success of this variant of the model is dependent on the availability of an efficient way to contact the participants—such as the web-based portals that several of the projects discussed earlier have developed. However, the development of such portals requires a considerable up-front capital investment that many researchers and research institutions may not be able to afford.

Model 3: *Obtain consent to return of specific categories of incidental findings at the time of—and as a condition of—enrollment (a "mandatory return" model)*

Up to this point, the models have been based on the assumption that participants will be able to choose which incidental findings to receive—at least within those categories of reportable results specified in the protocol. However, a recent set of recommendations by the American College of Medical Genetics and Genomics,[29] although made specifically with regard to clinical genomic testing, suggests a different approach in genomic research as well.[30] The ACMG recommended that at the time of consent to clinical genomic testing, regardless of the indication, patients be told that certain categories of actionable findings (mutations in fifty-six genes were specified, although the ACMG held out the possibility of revising the list in the future) would be returned automatically. The rationale for the recommendation was that actionable findings from other medical testing (such as radiological studies), even if made incidentally, are routinely provided to patients' clinicians, so that appropriate measures can be pursued to protect patients' well-being. The authors of the ACMG recommendations urged that genomic testing be considered in the same light as other medical tests and that laboratories report the specified categories of findings accordingly. A variant of this approach might involve informing participants that some actionable results will be returned, without necessarily limiting returnable findings to a particular list of genes; or the indications for mandatory return could be expanded to include selected findings with implications for the potential offspring of reproductive-age participants (for example, identification of serious X-linked recessive disorders in female carriers).

The ACMG's recommendations have attracted a good deal of reaction, pro and con,[31] and their application to genomic research, in which researchers may have different duties toward participants than clinicians do toward patients, is arguable. (We acknowledge that the boundaries between research and clinical care blur in many genomic studies, especially when the goal is to test the utility of genome sequencing as part of clinical care.) However, advocates of this model can point to a number of benefits. The consent process at the time of enrollment will be simplified because potential participants will not need to make choices about which results they will receive. They can be told simply that certain findings will be communicated, and if they are discovered to have the mutations in question, additional information will be provided at that time. Researchers will have the clarity that many of them desire with regard to the precise scope of their obligations. People being recruited for such studies will retain a degree of choice: if the prospect of receiving results about, for example, potentially serious but actionable conditions is sufficiently distressing, then they can elect to forego participation. Indeed, that option may be more acceptable with regard to participation in a research study than in the clinical setting to which the ACMG recommendations apply, since research participants are less likely to be faced with the choice of giving up potentially useful medical care.

The primary downside of this model relates to its restriction of individual choice. Research participants cannot exercise discretion with regard to those findings they desire to receive and those they would rather not know about, leading to disclosures that could be both under- and overinclusive, given their preferences. A

woman with a family history of breast cancer may be well aware of her increased risk of breast cancer but have made a considered decision to avoid knowing whether she carries a mutation in one of the BRCA1/2 genes. Although many people might choose differently, the substantial percentage of women at risk who decline to undergo BRCA1/2 testing indicates that her choice is not unique.[32] However, if BRCA1/2 are on the list of incidental findings that will be returned to participants automatically (as in the ACMG recommendations), then her only option may be to forego participation. (A modification of this approach that allows participants to opt out of receiving particular findings has been adopted by the ACMG.[33]) Requiring agreement to the return of certain results as a condition of participation may therefore diminish the willingness of some people to enter genomic research. When that research offers unique opportunities to advance individual health, as may be the case in studies of the implementation of genomic medicine, then both the person and society may be worse off if participants are deprived of choice. Moreover, this model shares some of the problems associated with the traditional consent model: considerable information about possible findings and how they would be dealt with will need to be provided as part of the original consent process.

Model 4: *Refer participants to third parties for consent and return of incidental findings ("outsourced" model)*

The first three models assume that investigators in genomic research studies will decide which incidental findings to make available to participants and will at some point seek consent of some sort for return of those findings. However, an entirely different approach can be envisioned that places the discretion to determine which results to receive in the hands of participants themselves. Several of the respondents to our survey of genomic investigators suggested that participants be given the raw data from their genome sequencing, perhaps on a USB drive. They would be told that they could take the data to a genetic specialist of their choosing and, with that person, decide which, if any, results they choose to receive. In essence, this model outsources the data analysis and consent process to genetic experts outside the research team.

The reasons this approach may be appealing to investigators are evident in the many concerns expressed in the literature and by the researchers we surveyed and interviewed about the time and cost likely to be associated with the return of incidental findings.[34] The traditional and staged consent models described above require that detailed information be provided to participants so that they can decide whether to consent to receive results, and even the mandatory return model requires some degree of additional disclosure. Screening for and interpreting reportable incidental findings—however they may be defined in a given study—require substantial time and effort, especially when the variants detected have not previously been reported or their significance is uncertain.[35] Once identified, research findings may need to be confirmed in CLIA-certified laboratories, at additional cost to the project. Recontacting participants is likely to be time-consuming unless an investment has been made in an online system. Communicating results to participants may be difficult for investigators who are not clinically trained, requiring them to hire additional clinical staff, and even clinician-investigators will be forced to spend time that might otherwise be devoted to advancing the research; communicating results without a clinical infrastructure in place to help participants contextualize the data and follow up on subjects may actually be harmful. All of these costs can be avoided by simply turning the data over to participants and allowing them to proceed as they choose.

Participants may also find advantages in this approach. Their decision-making about participation in a genomic research study will be simplified by separating it entirely from the question of whether they desire return of incidental findings, a burden that some participants may find overwhelming. They may still have to be told something about the nature of potential incidental findings and the information they will receive, but more detailed information could be transmitted in written form when the raw data are provided. The choice about which results to look at will be in the hands of those who choose to participate in the study. People who are averse to information about health risks can put the USB drive with their sequence data in the back of a desk drawer and forget about it or retrieve it only at some later point, when the information it contains may be relevant to a particular medical decision. Those participants who choose to know something about the findings will no longer have to rely on the investigators, who may not be well-informed about the implications of the full range of findings, and can instead choose an expert they can trust to interpret the data. Finding such services right now may not be easy, but if a substantial number of researchers (and perhaps even clinical centers) adopt this approach, then services are likely to emerge to meet the demand, in a way analogous to the current commercial availability of direct-to-consumer genomic testing. Moreover, such services will have an incentive to employ staff with strong communication skills, which some researchers may not have.

For all the advantages of this model, there are also some deeply unsettling aspects to it. At least for now, participants may not have access to resources for appropriate interpretation of raw genomic data, allowing the research team to avoid the burdens of returning incidental findings without realistic alternatives being available. Moreover, given that interpretive services and confirmatory testing (which may be necessary for research data generated in facilities

that lack CLIA-certification) are likely to be costly, poorer participants may be unable to afford them, creating an issue of social equity in the treatment of research participants and accentuating disparities in our health care system. Participants will need to incur that cost before they know the likelihood that a potentially useful (or indeed any) incidental result exists. If, as some have argued, researchers acquire ancillary obligations to the participants in their studies,[36] which may extend to the return of actionable information, then insofar as these responsibilities are outsourced, investigators may fail to fulfill their duties to participants.

Picking a Model

None of the possible models for informed consent to return of incidental findings in genomic research is ideal. Each has advantages and disadvantages, presenting investigators and IRBs with complex choices. How might decision-makers choose among them? We suggest two criteria that might be considered—consistency with researchers' ethical obligations and practicality—and we illustrate how they might be applied.

Criterion 1: *Consistency with researchers' ethical obligations*

The ethical obligations of researchers are generally recognized, at a minimum, as reflecting the duties of respect for persons, beneficence, and justice.[37] In the context of consent for genomic studies, respect for persons at least requires the provision of sufficient information for participants to make informed and meaningful choices. All of the models are consistent with that goal. But something more may be required by respect for persons than merely providing the information: a disclosure process that affords participants a reasonable opportunity to comprehend the information being provided. In the end, identifying this process rests on an empirical question: which model best educates participants about the choices they face? Although we now lack the data to answer that question, there are a priori reasons to be concerned about the traditional consent, mandatory return, and outsourced models in this regard. In the traditional consent model, even if the model is optimized by providing additional educational materials in advance or by allowing a more extended period for participant education, participants will be expected to assimilate and make choices based on a large amount of information that relates both to the primary study they are being asked to consider and to the possible return of incidental findings. The ability of most research participants to do that appears questionable. By depriving participants of the opportunity to choose whether to receive incidental findings, and which to receive, the mandatory return model limits their decisional autonomy, a prime consideration in respect for persons. Finally, although the outsourced model maximizes participants' choices, unless participants can be directed to reliable interpretative services, the outsourcing approach leaves investigators uncertain as to exactly what information will be given to participants by the services to which they turn; if potentially actionable data that would have been disclosed by the investigators is not identified by the interpretive service, this approach may leave participants without the information they need to take appropriate protective measures.

Beneficence in the research context has been described as the duty to "maximize possible benefits and minimize possible harms."[38] Each model envisions returning potentially useful results to participants, thereby meeting one of the desiderata of beneficence. However, the mandatory return model limits the scope of possible benefits by an a priori decision to restrict return of incidental findings to those that the investigators consider sufficiently medically actionable. Although medical knowledge that allows the implementation of prophylactic measures is obviously valuable, it is clear from interviews with research participants and with members of the public that they see benefits in obtaining other classes of information as well.[39] For example, data that are helpful for reproductive decision-making for participants or their children are highly valued, and many participants would also choose to receive pharmacogenetic information. Indeed, even incidental findings identifying risks for unpreventable and untreatable disorders (such as Alzheimer's disease) can be useful to people who desire to incorporate such information in major life decisions.

The minimization of harm component of beneficence might be met both by providing information that allows participants to take protective measures against identified medical risks and by avoiding the psychosocial harms that may be associated with the receipt of upsetting genetic information. Those two considerations may be in tension with one another, since some participants may be upset by data that in principle would allow them to take more effective prophylactic or treatment measures. Each of the models deals with this in some way: the traditional and

> The effectiveness of some of the models depends in part on funding to create the infrastructure on which they depend.

outsourcing models put the decision about how to balance these considerations in the hands of participants, thus reducing the risk that they will receive information they would find upsetting, whereas the mandatory return model leaves the decision to the researchers, thereby decreasing the risk that actionable information will not be revealed. Staged approaches allow participants to retain control, but when a decision is deferred until findings exist, the door is open to communication of unwanted information about potential risks. Neither giving priority to avoiding medical risks nor favoring the avoidance of psychosocial risks is necessarily superior; choosing one over the other depends on how one weights the two sets of concerns.

Justice in the research setting usually has been understood as relating to the fair distribution of benefits and burdens.[40] Here, the outsourced model raises particular concerns. By outsourcing the consent process, along with the interpretation and reporting of incidental findings, this model reinforces the disparities in access to medical services based on wealth that characterize much of our health care today. Participants who can afford to seek out private services to interpret the genomic findings will have the benefit of such information. Poorer participants, who make the same contribution to genomic research, will be left only with a USB drive containing what is, for them, uninterpretable and therefore useless data. It should be noted as well that under any of these models, participants without health insurance coverage or other resources to take advantage of the information they receive may similarly be deprived of the benefits that their incidental findings could convey.

Criterion 2: *Practicality*

Practicality is yet another consideration in judging these models. The effectiveness of an enhanced version of the traditional consent model and of the staged consent model depends in part on the availability of funding to create the infrastructure on which they depend: educational materials, including video and multimedia resources for traditional consent, and a system for communicating with participants, soliciting preferences, and returning information over time for staged consent. From the researcher's perspective, outsourcing may seem the most practical, since it removes the burden of dealing with incidental findings from the research team. However, in the absence of readily accessible interpretive genetic services, the outsourced model cannot function at all. To some extent, the availability of resources to interpret genomic data, now the most costly aspect of genome sequencing,[41] and to deliver the findings to participants in a sensitive and understandable manner affects all of the models. As better pipelines based on improved databases and bioinformatic algorithms are developed to identify pathogenic variants, so that the burden on researchers of interpreting the data diminishes, the attractiveness of mandatory return of a limited set of findings may fade. The outsourcing approach may become less attractive for the same reason, although there may still be an advantage in turning to experts skilled in discussing genomic findings with participants.

The Next Step

There is for now no optimal solution for the dilemma of how best to obtain consent for return of incidental findings in genomic research. Clarification of the relative virtues of the various models—and the hybrid models that are likely to develop—will depend in part on researchers' evaluations of their efficacy—work that would appear to be the next logical step in this area. Among the variables that might productively be explored in future research that compares these models are the nature and scope of information communicated; participants' comprehension, ease in decision-making, and satisfaction with the process; and the time and resource burdens on researchers and prospective participants. But selecting an approach also requires consideration of normative implications, and here, trade-offs are inevitable. Finally, in this rapidly changing area of research, new and better models for consent may develop, and as genomic research evolves, the balance of practicalities is likely to change as well. No one model is likely to represent the permanent solution to the challenges of obtaining meaningful consent for the return of incidental findings.

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References

1. Historically, the relevant policy discussion has used the term "incidental" to denote findings that were beyond the primary aim of the research. The idea was that, in the course of investigating disease A, a researcher might stumble upon a finding associated with disease B. Some genomic findings are "incidental" in that sense. But the new sequencing technologies, which entail the application of filters to raw sequence data, are moving us rapidly toward a time when, while one is investigating A, one can, at virtually no additional cost, look for variants associated with diseases A through Z (see E. Parens et al., "Incidental Findings in the Era of Whole Genome Sequencing?," *Hastings Center Report* 43, no. 4 [2013]: 16-19). When one is actively "filtering" or searching for mutations in genes other than those associated with the primary aim of the investigation, we think that the term "secondary" is more accurate than "incidental." Indeed, in the recent report *Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Context* (Washington, DC: Presidential Commission for the Study of Bioethical Issues, 2013), the Presidential Commission for the Study of Bioethical Issues argues for the importance

of making the distinction between incidental and secondary findings. However, given that "incidental findings" is the term that was used in the studies described below and remains the dominant term in the literature (see L. G. Biesecker, "Incidental Variants Are Critical for Genomics," *American Journal of Human Genetics* 92 [2013]: 648-51 and J. P. Evans, "When Is A Medical Finding 'Incidental'?," *Genomics in Medicine* 15 [2013]: 515-16), we use it in this paper, despite its limitations.

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