Appendix 1: IRP Secondary Findings Committee Report

EXECUTIVE SUMMARY

The Committee was charged with the task of developing an intramural-wide policy for the management of secondary and incidental findings* from exome and genome (hereinafter referred to as genome or genomic) germline sequencing. The Committee has considered guidance from The Presidential Commission on the Study of Bioethical Issues (PCSBI) report on incidental findings, the Recommendations from the American College of Medical Genetics and Genomics (ACMG) on incidental findings, and other relevant publications.

The Committee concluded that this is an important issue for the Intramural Research Program (IRP) because genomic and other high throughput technologies will grow in their clinical application and utility over time, and are certain to give rise to secondary and incidental findings. The Committee accepted the PCSBI recommendation that researchers should have a plan for handling secondary and incidental findings that are discovered in the conduct of their research. The Committee also accepted the PCSBI determination that because researchers have ethical obligations to research participants and a responsibility to develop generalizable knowledge, their obligations to deliberately seek secondary findings outside of the primary purpose of their research are less extensive than clinician's obligations. Consequently, the Commission concluded - and we agreed - that researchers should carefully consider this issue but that there is no general or universal obligation for researchers to actively search for such genomic findings. At the same time, the Committee recognized that there are context-dependent obligations that researchers incur in the process of performing different kinds of research. The greater the degree that the participant-researcher interaction resembles a clinical care relationship, the greater the obligation of the researcher to return secondary and incidental findings that are of high clinical utility.

Recommendations:

1) Intramural researchers performing human germline genomic sequencing should describe in the protocol their plans for identifying known pathogenic variants that are outside of, or beyond their research aims.
2) IRBs should review protocols that include germline genomic sequencing to ensure that secondary and incidental findings plans are appropriately addressed.
3) The informed consent process should clearly delineate how secondary and incidental findings will be handled. The IRB may determine that participants should be given the option to opt out of return of incidental findings or analysis of secondary findings.
4) The NIH IRP should support its investigators by establishing a central resource that will provide the analysis, confirmation, and return of secondary variants from a defined list of genes for protocols where the IRB determines this is appropriate.
5) The intramural NIH approach to secondary and incidental findings should focus only on variants that are of the highest medical relevance.

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* See body of report for definitions of these terms

RECOMMENDATIONS AND DISCUSSION

Scope and Key Terms Used in this Report

These recommendations apply to germline genome and exome sequencing, by which we mean the genome of cells that reflect the genome of the fertilized embryo, and not to somatically mutated genomes, such as those found in malignant cells. Although it is advisable for investigators to have an IRB-approved plan for handling incidental findings that might be generated by genomic technologies other than sequencing, these recommendations do not necessarily apply to transcriptome sequencing, nor do they specifically address issues of genome-wide array-comparative genomic hybridization (CGH) and single nucleotide polymorphism (SNP) genotyping. Arguably, copy number variations (CNVs) can yield secondary or incidental findings (see Table 1 for definitions) that are equally important and ethically compelling as those associated with variants detected by genomic sequencing. Furthermore, some genotyping chips that are now in use include high penetrance variants for disorders with high medical relevance. Indeed, non-molecular biology evaluations can incidentally detect susceptibility to serious genetic disease, so genomic technologies are not unique in this respect. However, these recommendations are intended for germline genome and exome sequencing and may or may not be applicable or adaptable for the other tests or evaluations described above.

The Committee adapted the definitions of findings from the taxonomy proposed by the PCSBI for the purposes of this report (below)

Table 1: Definitions and Examples of the Categories of Findings from the PCSBI Report – Adapted for Genomics

TYPE OF FINDING	DEFINITION	GENOMIC EXAMPLES
Primary Finding	Researcher aims to discover the cause of A, and the identified variant is relevant to A.	In a child with autism, genome sequencing identifies a CNV in a gene known to cause autism.
Incidental Finding: *Anticipatable*	Researcher aims to discover the cause of A, but learns B, a result known to be associated with the test or procedure at the time the test is administered.	Discovering misattributed paternity from nuclear family trio sequencing.
Incidental Finding: *Unanticipatable*	Researcher aims to discover the cause of A, but learns C, a result not known to be associated with the test or procedure at the time it takes place.	Newly described, unambiguously pathogenic variant is found a year after the gene sequencing was performed.
Secondary Finding	Researcher aims to discover the cause of A, and also actively seeks D per expert	A directed search is undertaken for pathogenic variants in the ACMG 56 gene list.

	recommendation.	
Discovery Finding	Researcher aims to discover the cause A through Z by employing a test or procedure designed to detect a broad array of results.	A genome sequencing study is undertaken with a research goal to identify any and all disease susceptibility variants that may be present.

We recognize that this terminology may be foreign to researchers and that the categories defined by the PCSBI may dichotomize results and research scenarios where there may well be a spectrum of results that cross the boundaries of these definitions. The key attributes that we focused on were to distinguish variants that relate to specific research aims of the study from those unrelated to the aims of the study (primary vs. secondary and incidental) and to distinguish among the latter two categories of variants as to whether they are deliberately sought vs. inadvertently encountered (secondary vs. incidental).

Background for this policy

The Committee determined that it is essential for the NIH Intramural Program to have a consistent, understandable, ethically grounded, but flexible approach to the issue of secondary and incidental genomic findings. Two apparently contradictory issues were recognized – both the inappropriateness of a one-size-fits-all approach to this issue in the research context and the unacceptability of highly similar research protocols having widely disparate approaches to this issue. The Committee strongly endorsed the notion that the interaction of the investigational review board (IRB) and the principal investigator (PI) is the best place to reconcile these sometimes-competing issues. For IRBs and PIs to have the authority to best decide how to handle this issue, it is essential that they have both the technical capacity and the resources to effectively implement their decision regarding how secondary and incidental findings should be handled. To this end, we recommended a process whereby the IRP can support the identification and return of these findings, which is discussed below. This entire policy proposal is dependent upon the future availability of this currently unavailable support. The key decision is whether to seek secondary findings, and then specifying the mechanisms for how secondary findings and incidental findings will be managed. We discussed secondary and incidental findings separately, but later discuss how they can be similar in some ways.

As described in table 1, the PCSBI has distinguished secondary from incidental findings. A key distinction is that secondary findings are deliberately sought whereas incidental findings arise unexpectedly and can be of an unpredictable nature. The Committee recommended a stratified approach whereby the PI and IRB first determine if it is appropriate to evaluate sequencing data for secondary findings and then evaluate how incidental findings should be handled. We therefore divided this discussion of our recommendations into two separate sections, the first on secondary findings and the second on incidental findings. Finally, we close with two issues that are generic to both approaches.

While this report focuses on the management of secondary or incidental findings in research participants, it is critical to recognize that the potential benefits of such a finding may accrue to the relatives of the research participant, including those not involved in the research. Therefore, PIs and IRBs need to take into account the interests of these relatives when evaluating these considerations.

Which studies should return secondary findings?

The Committee determined that the more a research protocol resembles a clinical (doctor-patient) relationship, the greater the obligation of the researcher to participants vis-à-vis secondary findings. This determination was a recognition that human subjects research comprises a spectrum of activities that range from the most basic to those that in many respects are practically indistinguishable (from the participant's perspective) from a clinical encounter. Indeed, some IRP research protocols provide substantial clinical care and services in the course of their research interactions with the participants. We recognized that inherent in this concept is the risk of conflating the purposes of research (i.e., to contribute to generalizable knowledge) with that of clinical care (i.e., to treat an individual patient with his/her best interests in mind). The Committee acknowledged that it is critical for IRBs and investigators to be aware of this risk and to ensure that the informed consent process clearly addresses the difference between participation in a research study and receiving care in the context of a doctor-patient relationship, and the plan for returning secondary findings. More specifically, we acknowledged that a reasonable person participating in a study, especially one involving clinical care activities, might well expect or assume that a potentially life-saving finding would be addressed in a way that protects their interests and welfare.

We recommended that the question of whether secondary findings should be sought or reported for a given research protocol should be determined by the PI and the reviewing IRB. Together, they should assess each protocol to evaluate the appropriateness of the plan for identifying and returning secondary or incidental genomic findings. Research protocols are expected to have varying combinations of attributes that argue for or against return of secondary and incidental findings, further underscoring the need for a nuanced, study-specific, rather than a "one-size-fits-all" approach to how secondary and incidental findings should be handled in the research setting. To this end, we have proposed a list of attributes for investigators and IRBs to weigh in their deliberations.

Table 2 Attributes for IRBs and PIs to consider when deciding whether a protocol should search for secondary findings.

Attribute	**Argues *for* deliberate search for secondary findings**	**Argues *against* deliberate search for secondary findings**
Nature of the relationship between investigator and	Investigator knows participants and provides some clinical care or	An anonymous sample donor

participant	information. Participants regularly visit the NIH-CC	
Nature of the Study, including: 1. objectives and aims of the research protocol 2. procedures or processes the participant undergoes at NIH	The research protocol is investigating a primarily clinical question The study involves clinical evaluations and tests and participants receive their results	The research protocol is investigating a basic science (or technical?) question The study involves no clinical testing or evaluation
Timeliness of the findings	Sequencing analysis is done while participant is actively involved in research	Secondary findings are generated many years or even decades after participant's active involvement
Nature of the Study population, including: 1. Expected Relevance to current situation 2. Other reasons the population may want or not want findings	Study population in a position to find secondary results useful Important for family or cultural reasons	Study population has terminal illness and short life expectancy Cultural reasons argue for not returning certain findings

These attributes are complex, and none individually should be considered determinative of whether secondary findings should be sought. While different IRBs may not come to exactly the same conclusions (especially in the early implementation of these recommendations), it is our expectation that over time, IRBs will become comfortable and reasonably uniform in this determination. If the IRB makes a determination that secondary findings will not be sought, the consent form should make clear to the participants that no effort will be made to identify medically important gene mutations outside the focus of the study, even if such findings might be life-saving. The PCSBI report emphasized that transparency and communication with participants is a core value upon which management of secondary findings should be based.

Which variants should be returned?

The Committee acknowledged that there are few data and little consensus regarding what the threshold for returning secondary genomic findings in research should be, but it is certain that the assessments of where to draw this line will change rapidly in the future. At the same time, it is highly likely that there are genetic variants for which almost anyone (researcher, ethicist, or research participant) would agree that disclosure to a research participant is the right thing to do. Consequently, there is an emerging consensus in clinical care and in some research contexts that genomic findings that are analytically and clinically valid, clinically

significant, and clinically actionable should be returned to participants. The Committee also recognized that there are some who feel that all potentially relevant findings (including findings that have only personal utility and not strictly medical actionability) should be returned to participants. Based on these competing views regarding the management of secondary findings, the Committee concluded that intramural investigators and IRBs should begin by addressing only those genomic variants known to have the highest medical utility, learning how to effectively address these, and then expanding or contracting that approach over time, based on experience and accumulated data.

The sufficiency of the sequencing and analysis process is an important determinant of how secondary findings should be managed. By sufficiency, we mean the sensitivity of the entire process for variants that indicate a substantial risk to an individual for the conditions or the genes that are assessed. Currently, a key feature of managing secondary findings is the evaluation of the data that have been generated to identify what is present among those data, an approach that has been termed by some as opportunistic screening. In this strategy, there is no effort or obligation to generate or evaluate more data than the process naturally produces. This is a very different approach compared to diagnostic molecular testing, which is a directed and thorough assessment of a gene (or panel of genes) to identify as many pathogenic or potentially pathogenic variants as may be relevant to the diagnostic question. Opportunistic screening for secondary findings should have a relatively high positive predictive value (the likelihood that the participant actually has the variant that the sequencing indicates and this variant is pathogenic) to counterbalance the low prior probability that the participant has the disease or susceptibility. Therefore, this process makes an explicit value judgment to favor the positive predictive value and pathogenicity of the variant over sensitivity and completeness of the search for possible secondary variants. Investigators and IRBs need to be cognizant of this tradeoff to ensure that participants understand that such a screen is not a substitute for a comprehensive, directed gene-specific (or gene panel) test, if that is otherwise clinically indicated. If a gene or gene panel test is clinically indicated, the participant would need to seek this outside of the research setting. The implications for informed consent are described below.

A resource for analyzing and returning *secondary* findings

When a PI and IRB determine that secondary findings should be sought and returned, a mechanism must be available to facilitate this process. It is not reasonable to expect all researchers who perform exome and genome analysis to be able to identify and manage such findings. Indeed, some PIs who include genomic sequencing in their research are not clinicians, most PIs are not knowledgeable about all of the genes and disorders that might warrant consideration for return, and some research teams do not include any clinicians who could return such a result to a participant with an appropriate level of medical and genetic counseling. It was the Committee's view that it is the role of the NIH IRP to support and encourage genomic research by providing the resources necessary to address this challenge. To that end, we proposed that stakeholder NIH IRP institutes, in collaboration with the NIH Clinical Center, develop a centrally-funded resource through which

PIs can submit to this service a list of all variants that they have identified through their research-based genomic sequencing that are in a list of candidate genes approved by the Secondary Findings Service.

We envision that such a service would offer the following support to IRP investigators. 1) establish and maintain a list of the genes that the service will analyze so that investigators can in turn provide to the service the list of all candidate variants in those genes that were identified in their research sequencing 2) interpretation of the submitted variants to determine which, if any, meet a reporting threshold as a secondary finding 3) clinical support services to contact participants to arrange for resampling and to perform Clinical Laboratory Improvement Amendments (CLIA) testing to validate candidate deleterious variants 4) NIHCC-based clinical consultation with participants who have positive findings to provide medical and genetic evaluation, counseling, and assistance with referrals for follow up care.

We recognized that establishing such a service in support of the IRP would be novel and innovative, given that there are few precedents for a program of this nature. The Committee concluded that the NIH IRP is the ideal milieu for this exploratory approach to a difficult challenge. Recognizing this, the Committee strongly recommended that continual assessment of the cost, yield, and efficacy of the service, participant outcomes, etc. should be an essential part of this program. This will allow the IRP to learn as the program is developed, improve what works, discontinue what does not, and generate knowledge and experience for the clinical genomics community in fulfillment of the core mission of the NIH.

Facilitating the availability of study participants for post-test medical and genetic evaluation and counseling is a major logistical challenge to the proposed approach to secondary findings. For participants who are not nearby NIH, repeat sampling for CLIA testing could be performed by having samples shipped to NIH by the participant or a local outpatient clinical laboratory. For those who are able and are willing to travel, it would be ideal to offer them the opportunity to return to the NIHCC for this evaluation and counseling in person. It is a more difficult question as to whether the NIH should offer to support their travel expenses and this issue deserves more study. For participants who cannot return to the NIHCC for this evaluation and counseling, the Secondary Findings Service could work with the participant to help them identify a local or regional health care provider to whom the results could be transferred and the participant could receive the result from this provider at their own expense. Alternatively, the Secondary Findings Service could develop approaches to this care, such as telemedicine, to enable remote medical evaluation, counseling, and care.

The Committee concluded that consent form check boxes and the possibility of participants or researchers selecting among the secondary findings that may be returned is impractical. One concern was that such customized approaches are logistically challenging, error-prone, and cumbersome for researchers. Another concern was that customized preference setting presumes an extremely sophisticated research participant, a highly detailed and information intensive encounter with a clinician versed in all of the disorders under consideration, and the potential for amendments to such decision making over time. Perhaps in the future, sophisticated decision making processes and customized sequencing may make such approaches practical, but

the Committee concluded that a uniform, single approach to a genomic interpretation package was the most realistic approach.

The Committee felt that NIH must also address the issue of how to disclose negative secondary findings while conforming to CLIA requirements. It would be important to issue some form of communication to the PI and participant upon completion of the analysis, whether the findings are positive or negative, as the PI has a clear interest in knowing that the analysis was indeed completed (and not mislaid or neglected). To conform to the CLIA regulations by communicating only validated, individual results to research participants, we propose that the PI be provided with a written communication that the secondary findings analysis was performed according to the then-current gene list and that there were no results found on the analysis that met the standards for reporting. It is our view that it is the responsibility of the PI to communicate that message to the participant using whatever means they and their IRB conclude is most appropriate for their study. However, it was not felt to be appropriate for the central NIH Secondary Findings Service to enter such a negative result into CRIS or for the PI to provide a written report of a negative secondary finding analysis because that analysis would be based on non-CLIA sequencing and could be misconstrued as an actual negative diagnostic test result.

The development and maintenance of a list of genes for which secondary findings should be sought will be an important part of this effort. While there are several existing lists that may be useful to implement for a secondary findings evaluation (e.g., Refs [1, 2] the IRP should develop a process for establishing and curating such a list. This process should be transparent, deliberate, and should properly balance the need to disclose potentially life-altering findings with the need to limit the clinical burden of this activity. Once such a list is established, it is certain to evolve over time. The IRP will need to have a process that monitors developments in the field of incidental findings and adjusts the list over time to be responsive to those changes. We do not believe that researchers who use the Secondary Findings Service that is based on this list need to amend their protocols solely because the list has added or deleted genes.

The Committee recognized both that the state of current knowledge with respect to secondary and incidental findings is incomplete, and that the related technology and clinical recommendations will evolve rapidly. To this end, the Committee felt that it would be essential to implement quality control and quality assurance (QA/QC) follow-up assessments targeting the participants who undergo secondary findings analysis. The program must also be sufficiently dynamic and flexible to respond to changes in technology or management recommendations. This program must have measurable performance benchmarks for performance, and it must evolve in response to challenges and deficiencies that are identified through ongoing QA/QC activities. To optimize the usefulness of the proposed program, it will be essential to receive feedback from participants who have undergone the analysis and those who have received results. As well, the service should communicate regularly with PIs to determine if the service is meeting their needs and how it could improve. To this end, investigators would be asked to provide research participant contact information to the program to allow follow-up surveys and/or interviews.

An approach for analyzing and returning *incidental* findings

One challenge that IRBs and PIs will need to address is a plan to handle findings for protocols in which it is determined that secondary findings should not be sought and handled by the process described above. In this scenario, it remains possible that a highly medically relevant variant could be present within a genome or exome and may be inadvertently identified or 'stumbled upon' by a member of the research team. According the PCSBI definitions, this would then become an anticipated incidental finding. The Committee generally felt that this was an undesirable situation in that it reintroduces elements of arbitrariness and inconsistency into the analysis and disclosure process (because such a finding might occur in one participant and not occur in another participant by chance alone, when in fact both participants might harbor a equally medically relevant variant). The Committee identified three potential approaches to this scenario that PIs and IRBs could consider:

1) Recognize that incidental findings will occur and return medically relevant results to participants *ad hoc*, or
2) Do not return incidental findings to participants, or
3) Delete or avoid generating variants in what are recognized to be secondary findings genes

The Committee again concluded that a "one-size-fits-all" approach was not appropriate here. We were unable to prescribe a generally recommended approach to this issue for all protocols and recognized that all three possible approaches had significant limitations and challenges. This is not to say that all are equally plausible or appropriate, and the comments below reflect the views of the committee regarding their relative merits.

Return of incidental findings to participants

This approach is currently used by many investigators, which is one where a variant might be stumbled upon (rather than deliberately sought) in a genome or exome that is associated with a disease and the variant is apparently pathogenic. The team would be required to do some background research (literature research and evaluation of variant databases) to affirm that there is reason to believe that the variant is pathogenic and the disorder is sufficiently medically important to warrant consideration for return. An alternative or supplementary approach would be to consult with gene or disease experts about the variant. If they determined that the variant did warrant consideration for return, the PI would engage with the IRB to determine if, and if so how, the result should be validated and returned to the participant.

There are a number of potential issues with this approach. The first is that it is highly arbitrary, at several levels. The variant identification would be a random or arbitrary event – by definition the variant is identified by chance. It would also be an obligation of the team and downstream users of the data to not deliberately seek such variants, as that would constitute a secondary findings analysis, which should have been reviewed and approved by an IRB. Once the variant is identified, the process of investigating the variant to determine if it rises to the level to justify return would likely be outside of the expertise of the researchers, which could

introduce additional arbitrariness and inefficiency. It would seem likely that different investigators would make different decision with the same variant. Finally, taking this to an IRB could lead to additional inefficiency to the process.

The committee considered whether this approach to incidental findings should be managed through a centralized clinical reporting resource (similar to that of the Secondary Findings Service proposed above) or whether this should be the responsibility of the PI (as it is currently). The centralized approach has some similarities to the secondary findings approach outlined above and using such an approach could have merit. There are some potential logistical challenges, primarily that of the potentially large number of such findings, the mechanism for how these would be submitted and filtered, etc. The committee did not resolve this issue with some members favoring the centralized approach but others opposed. This will deserve further study and consideration.

No return of incidental findings

This approach is simpler in many respects than the previously described approach. Researchers whose plan, approved by the IRB, was to not seek secondary findings would simply be precluded from returning any variant, regardless of how medically compelling this result might be.

There are a number of issues with this approach. The first is that there is a developing consensus to "never say never" with respect to how research participant data will be managed. To permanently preclude the ability to ever go back to a participant can create ethical challenges downstream that are difficult to anticipate and may be regrettable. In addition, the ability of the research team to identify such variants without the possibility of returning them may lead to distress among the researchers. Most importantly, this approach precludes the potential ability to save a participant's life, with its dire direct implications and the indirect consequences for the research enterprise.

Non-generation or deletion of potential incidental findings from exome and genome data

It is possible to either not generate or delete data beyond those needed to address the primary research question. For example, one could design an exome capture that did not select for any of the genes recognized to be important secondary findings. Alternatively, all genes could be captured but those that included medically relevant incidental findings could be informatically deleted from the data.

The committee identified a number of serious issues with this approach. The first is that it is antithetical to good genomic science, which is to evaluate and consider all variation as potentially relevant to the scientific question. The committee was uncomfortable with the general idea of deletion of data, but did not go so far as to determine that it should never be used to address this issue. The second is ethical in that one could question the validity of an approach that attempts to solve a problem by pretending the problematic data do not exist. The third is that it may be impossible to prospectively identify and delete (or not generate) all potentially relevant incidental findings. Finally, like the second approach, it denies at risk individuals the

opportunity to learn potentially life saving information.

As noted above, the Committee recognized the limitations and problems raised by all three of these approaches, which was a primary motivator for this Committee to recommend the Secondary Findings Service approach, and recommended that careful planning will mitigate this possibility, and that such developments be considered on a case-by-case basis.

It is important to recognize that incidental findings may arise even if secondary findings are sought. For example, we can envision that a research participant may undergo a secondary findings analysis that is negative, and a researcher might stumble upon a finding in a gene that s/he concludes is highly medically actionable in spite of the fact that this gene is not part of the secondary findings analysis that the participant underwent. We view this as an anticipated incidental finding, which would need to be handled as above, with the investigator proposing return to the IRB (and/or an expert panel empowered by the IRB) and if approved, CLIA-validated and returned to the participant.

Conversely, if the IRB determines that a secondary findings analysis is not appropriate for a given study and there is a stumble on finding (assuming such data were not masked) in a gene that would have been included in the then-current secondary findings gene list, the investigator could approach their IRB to determine if it is appropriate to return such a result. If the IRB concurred, that finding could be forwarded to the Secondary Findings Service for evaluation, confirmation, and return to the participant via the process described above for secondary findings. This scenario should be rare – if it recurred within a given protocol it would beg the question of why the deliberate secondary findings approach would not be more appropriate. Another nuance here is that the incidental finding of a variant in a secondary finding gene list would only be reported to the participant by that service if it met the standards for reporting by the service. Were the investigator to have a lower threshold for pathogenicity, the Secondary Findings Service could decline to engage with the confirmation or return of that result. This is another example of why the Committee favored the prospective Secondary Findings Service approach to this issue.

It is challenging to envision a systematic approach to the issue of unanticipated incidental findings, because they would be heterogeneous in nature and difficult to plan for. Unanticipated incidental findings will need to be handled on a case-by-case basis, starting with the PI and the IRB. It would likely be beneficial for investigators to consult with the Secondary Findings Service regarding such findings. The challenges of this issue are discussed above. The Committee recommended that such issues be handled on a case-by-case basis, with IRB and/or bioethics consultation so that the IRP as a whole can learn from these occurrences and develop a thoughtful and systematic approach. Overall, the array of issues and challenges contributed substantially to the conclusion of the Committee that the secondary findings approach was generally preferable to the approach of stumbling upon incidental findings.

Two general issues

Opting out of receiving secondary or incidental findings

There are two approaches that investigators may use for secondary or incidental findings. Participants may be offered an opt out of the process of identification of secondary or incidental findings. An alternative approach is that investigators may make analysis of secondary and incidental findings routine and decline to enroll participants who do not wish to receive these results. As recommended by the PCSBI, an opt out necessitates that the informed consent process ensures that participants are well informed regarding what opting out could mean for their health and well-being. This engenders a substantial obligation on those performing the informed consent regarding IF/SF analysis. In some ways, a protocol that permits an opt out imposes a higher burden on the PI (and other staff who do the informed consent) than does a protocol where such analysis is routine. It may be challenging to ensure that a participant who has no family or personal history of the disorders related to the secondary or incidental findings has a good understanding of what they may be foregoing for themselves and their relatives.

In the event a researcher discovers a potentially lifesaving unanticipated incidental finding for a participant who has opted out of receiving secondary or incidental findings, they should generally honor the informed consent opt out by not returning the result. Any exceptions to this should be negotiated with the IRB.

Returning results to participants who may not have resources to implement care for such findings

The Committee struggled with the question of how to address secondary or incidental findings in protocols that may enroll study participants who do not apparently have access to medical care that would allow them to implement surveillance or treatment based on such a finding. This scenario creates a collision of the key values of justice, beneficence, and autonomy. While we could envision scenarios where it might appear to be unreasonable, or even pointless, to return such a result, we could identify no ethically justifiable alternative to the return of results in this setting, if it is otherwise justified. We concluded that it was ethically unacceptable to determine that results should not be returned based on this attribute, even as a contributing factor. Based on this reasoning, this attribute was left out of table 2.

SUMMARY

Addressing the numerous dimensions and considerations of findings that may emanate from exome and genome sequencing is a challenge. A key assumption of the Committee was that investigators want to do what is right for their participants, but are hindered by numerous barriers. Most importantly, there are potential direct harms to research participants and their relatives if this issue is not handled correctly. As well, the NIH, the field of genomics, and the research enterprise more generally could be subject to indirect harms if participants or their relatives suffer because of an unorganized or incoherent approach to this challenge. The complexity of this challenge led the Committee to conclude that there was no single, one-size-fits-all approach; rather, that there are a number of appropriate approaches, with different approaches for different studies. Our charge was to recommend an approach that recognized the heterogeneity of studies and simultaneously

move toward consistency across studies – studies with similar attributes should have a similar approach to secondary and incidental findings. A key finding in these recommendations is the recognition that there are studies where there are substantial clinical obligations and a substantial duty to warn. The Committee outlined factors that IRBs and investigators can use to make a rational decision on return of secondary genomic results. The Committee also concluded that in most cases where this obligation exists, it is highly desirable that this be performed in an organized, prospective, and consistent manner with robust informed consent. We have recommended that the IRP develop a Secondary Findings Consultation Service to accomplish this. We have also outlined three approaches that IRBs can take to incidental findings, but in doing so have recognized that the organized secondary findings approach has much to commend it and in many situations may be preferable to the incidental findings approach. The Committee members look forward to further engagement in this important debate and hope that these initial recommendations can help the IRP develop a robust approach to these findings, maintain the core values of human subjects protection, and allow intramural investigators to stay focused on their primary research aims.

Membership of the Committee:

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Richard Cannon, NHLBI
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