A Clinical Service to Support the Return of Secondary Genomic Findings in Human Research

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Human genome and exome sequencing are powerful research tools that can generate secondary findings beyond the scope of the research. Most secondary genomic findings are of low importance, but some (for a current estimate of 1%–3% of individuals) confer high risk of a serious disease that could be mitigated by timely medical intervention. The impact and scope of secondary findings in genome and exome sequencing will only increase in the future. There is considerable agreement that high-impact findings should be returned to participants, but many researchers performing genomic research studies do not have the background, skills, or resources to identify, verify, interpret, and return such variants. Here, we introduce a proposal for the formation of a secondary-genomic-findings service (SGFS) that would support researchers by enabling the return of clinically actionable sequencing results to research participants in a standardized manner. We describe a proposed structure for such a centralized service and evaluate the advantages and challenges of the approach. We suggest that such a service would be of greater benefit to all parties involved than present practice, which is highly variable. We encourage research centers to consider the adoption of a centralized SGFS.

Introduction

Exome sequencing and genome sequencing (ES/GS) are increasingly used in both clinical care and research primarily because of their power to identify the genetic etiology of disease.[1–3] However, ES/GS also generate secondary findings, previously referred to as incidental findings. Hereinafter, we adopt the terminology of the Presidential Commission and use the term "secondary."[4] As defined by the Commission, secondary genomic findings are those findings that are anticipated and can be actively sought with a given procedure, such as ES/GS, but are not the primary target of the research evaluation. Approaches to addressing the evaluation and return of secondary genomic findings in clinical practice have been extensively discussed and debated.[5–7] Although some resolution regarding secondary genomic findings has been achieved in the realm of clinical practice, approaches to secondary genomic findings discovered in the course of research studies are less settled, and practices are highly variable.[4,8,9] This variation in practice in the research community is problematic for research participants and leaves institutions, institutional review boards (IRBs), and individual research groups unclear about their obligations toward participants. Researchers and IRBs struggle with the issue of secondary genomic findings for many reasons, including debate over the boundaries between clinical care and research, concerns about the role of participant preferences, evaluation of risks and benefits to participants, limited institutional resources, and the lack of practical mechanisms for identifying and returning secondary genomic findings to research participants.[10–12]

A working group of NIH intramural scientists assembled to address this challenge. We first addressed two sets of questions: (1) whether ES/GS research studies should return secondary genomic findings and (2), if some should be returned, what should determine which research studies are appropriate for the return of secondary genomic findings, which findings warrant return, and how this information should be disclosed. We initially rejected two extreme options in response to the first question: (1) that all studies should return results and (2) that none should do so. We rejected option 1 because mandating universal return of secondary genomic findings might be inappropriate or highly impractical in some types of research studies. We

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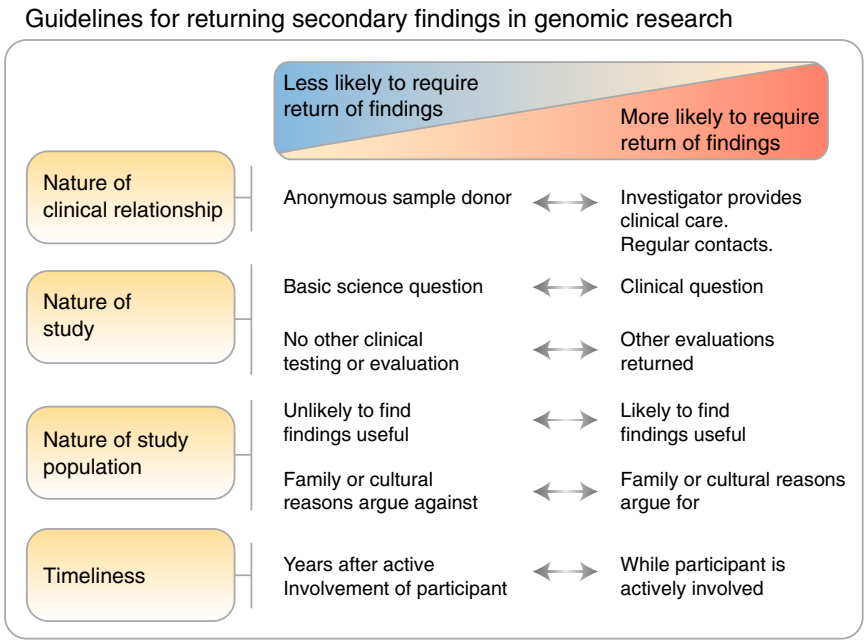

Figure 1. Graphical Representation of Some Key Attributes of Research Studies that Argue For or Against Seeking and Returning Secondary Findings

rejected option 2 because not returning research findings that might provide direct and easily derived benefits for participants would violate the principle of beneficence to research participants, in at least some cases. We therefore concluded that some ES/GS research studies should return some secondary genomic findings, which then raised another set of questions related to which studies should return secondary genomic findings, which findings should be returned, and how this should be accomplished. It is worth noting that we also considered and rejected the approach of deleting or masking data (e.g., the sequences of genes that could generate incidental findings). We concluded that this was antithetical to good genomic scientific practice, in that it potentially reduces the chance of discovering primary findings in genes that have pleiotropic effects (e.g., variants that might cause both dilated cardiomyopathy and skeletal muscular dystrophy).

We suggest that the IRB, in collaboration with the principal investigator (PI) of the study, is the appropriate body to determine which studies should return secondary genomic findings. The return of secondary genomic findings might not be appropriate for some research studies, even if it is practical. This should be established during the IRB review process. Some of the factors that could be considered include the timeliness, quality or completeness of the genomic analysis, relationship (or the lack thereof) between the investigator and research participant, potential importance to the subject (e.g., a risk allele in a study of individuals with a terminal illness), and others. We have outlined some factors that we believe to be germane to this determination in Figure 1. IRBs are well positioned to critically and independently analyze potential benefits and harms to participants of returning secondary genomic findings, the attributes of the study that favor or disfavor return, and the available resources for returning findings. The IRB can also serve to educate and inform researchers regarding their responsibilities and to standardize practice across research groups. By laying the groundwork for the return of findings whenever it is appropriate and feasible, we also wish to build a process that makes returning secondary genomic findings more practical and more common.

Currently, there is a disconnect between what both researchers and research participants say they prefer with respect to secondary genomic findings and what is actually occurring, which is reflected in survey data of relevant stakeholders. A minority of researchers (40%) reported they were either already returning a subset of secondary genomic findings or planning to do so in the future. In contrast, 95% of surveyed researchers agreed that secondary genomic findings should be returned to participants.[8] A wide range of genetic professionals hold the view that returning some secondary genomic findings from some types of studies is appropriate.[13–15] Furthermore, a substantial majority of research participants also consistently express a strong interest in receiving at least a subset of secondary genomic findings.[16–18] These data show a gap between researchers' desires and preferences regarding the return of secondary genomic findings and their current practice and show that participants generally expect the return of secondary genomic findings. We anticipate that creating the capability to return secondary genomic findings will alleviate a major concern about validating findings and counseling individuals about them and in turn shift the decision-making process toward favoring this approach. To address these gaps in capability, we propose a mechanism that will allow researchers to fulfill their expressed preference to return such results and to meet the expectations of the participants receiving secondary genomic findings.

A Proposal for a Consultation Service for Secondary Genomic Research Findings

To address these issues, we propose a secondary-genomic-findings service (SGFS) as a mechanism for converting ES/GS research data into analytically valid secondary clinical findings and providing medical and genetic counseling for those findings. This service would make available to PIs a service that would take research-grade ES/GS

Figure 2. A Graphic Representation of the Steps Involved in the SGFS
Abbreviations are as follows: IRB, institutional review board; PI, principal investigator; ES/GS, exome sequencing and genome sequencing; SGFS, secondary-genomic-findings service; EHR, electronic health record; and CLIA, Clinical Laboratory Improvements Amendment.

data, screen it for pathogenic variants from a specified gene list, resample participants with such variants, validate the variants in a clinically valid manner, and return the variants to the participants (Figure 2). The IRB would consider the PI's proposal for handling secondary findings and make a determination as to whether the protocol and the participants have attributes appropriate for the return of secondary findings (Figure 1). If the answer is affirmative, the IRB and PI would then work together to implement appropriate informed consent and a description of, including a protocol for, the process. The service would provide four main functions for researchers performing genome or exome research: (1) identify potential clinically relevant secondary findings from research data, (2) re-sample research participants, (3) confirm any secondary findings by clinical-grade testing, and (4) provide medical and genetic counseling for participants when providing information about findings.

In the case of a negative secondary-findings analysis, i.e., one in which no pathogenic results from the SGFS gene list are identified, it is challenging to address this issue while conforming to the Clinical Laboratory Improvement Amendments (CLIA) regulations that require communication of only validated results (a negative secondary-findings analysis of research data cannot practically be verified by CLIA). We propose that the service would provide the PI with a written communication that the secondary-findings analysis was performed according to the then-current gene list on a batch of ES/GS results and that no variants meeting the standards for reporting were found. It would be the responsibility of the PI to communicate that message to the participant by expressing only that there are no such results to report, which is distinct from saying that no variants are present. This is critical because in general, research ES/GS are not as sensitive as clinical single-gene or gene-panel testing. During the informed-consent process, PIs or research staff would need to explain to participants in advance that a lack of confirmed positive results does not necessarily mean that no pathogenic variants were present (in the scanned gene or elsewhere in the genome) and that the usual clinical indications for genetic testing (e.g., a family history of disease) still apply.

A key issue that needs to be addressed is the cost of such a service. These include immediate costs (e.g., the cost of identifying, validating, and communicating results to participants) and downstream costs (e.g., follow-up medical tests, genetic testing, and medical care). We estimate that the immediate costs would include resources to support (1) the time needed for the bioinformatician and geneticist to screen the submitted variants for the subset that is pathogenic and clinically actionable, (2) clinical re-sampling, (3) CLIA validation testing, and (3) the professional time necessary for the return of results. The costs of the service can be divided into those that are intrinsically part of the research enterprise and those that are clinical services. In the NIH Intramural Research Program (IRP), all such costs must be borne by the IRP itself, given that no clinical costs are currently billed to

third-party payers. We have estimated these costs under varying assumptions of the number of exome or genome sequences that are submitted and analyzed and then amortized that across all submitted sample files (that is, we divide the cost across all submitted sequences rather than charging more for positive findings than for negative findings.) These cost estimates range from $26 to $83 per exome (Supplemental Data). In the extramural community, the costs of the bioinformatician's and geneticist's review of the research sequence data would most likely not be billable as a clinical service and would similarly be borne by the institution as a research infrastructure cost, presumably supported by indirect funds or institutional research resources.

It is more difficult to estimate the downstream costs. The clinical services, which comprise the majority of the costs, could be billable as clinical services. The PI and the IRB would determine whether these clinical costs would be billed to the participant or insurer, charged to the researcher, or funded by institutional resources. It is difficult to estimate the potential downstream clinical evaluation costs with currently available data, but current estimates[19] suggest that it could be cost effective (see below). This question should be rigorously addressed in future studies.

We suggest that a SGFS should begin with a goal of returning variants from a relatively small list of genes for disorders that have the highest potential medical impact, perhaps starting with the list proposed by the American College of Medical Genetics and Genomics for secondary findings from clinical genomic testing[5] or one of those of other leading genomics research programs.[20] We believe there is value in starting small and scaling over time when implementing a novel strategy in order to garner experience with respect to costs, benefits, and potential harms of returning such variants to research participants. As discussed below, the ethical arguments of beneficence and duty to rescue are strongest for disorders that have the greatest potential medical benefit, which further justifies the expenditures necessary for accomplishing those research ethics goals. We acknowledge that research participants might desire more information than that included in the lists noted above, but for the reasons articulated below, we view that need as less compelling in the early days of our experience with this strategy.

Benefits Conferred by a SGFS

We suggest that implementing this SGFS would have substantial practical benefits. First and most importantly, the service would provide a standardized mechanism for potentially medically actionable genome or exome results to be systematically returned to research participants. Pathogenic variants in the genes included in secondary-findings lists are associated with severe or life-threatening disorders that are commonly underdiagnosed and for which there are effective medical interventions that can potentially reduce morbidity or mortality from the diseases or susceptibilities associated with secondary pathogenic variants.[5] Second, participating researchers would benefit from replacing what is now an arbitrary, ad hoc process with one that is potentially more uniform and equitable to research participants. Investigators would also be provided with a mechanism for returning important results, which they strongly endorse but are not resourced to provide. Third, uniformity in disclosure practices within an institution could avoid potential negative perceptions of institutions as being unfair or arbitrary. It is our hope that more research programs will be able to return secondary findings when this service is established.

Ethical Principles and the Return of Secondary Findings

Various commentators and organizations have identified numerous ethical considerations related to returning secondary findings in ES/GS; these include beneficence, the duty to rescue, respect for persons, justice, and non-maleficence.[21–23] Although each of these is relevant to decisions about returning secondary genomic findings, beneficence is the most compelling and relevant principle. This principle calls for maximizing benefits and minimizing harms and is one of the key principles underlying ethical research, as explicated in the Belmont Report.[24] In this context, identifying, validating, and communicating high-medical-impact variants from ES/GS research potentially provide substantial clinical benefit for participants. This benefit could be realized at a reasonable cost[19] and at apparently low risk for the participants.[25]

The duty to rescue requires that individuals take reasonable measures to help those who are in danger, such as individuals with actionable genetic variants that have clinical significance. Researchers who discover that an individual has such a variant might be in a position to rescue that individual from the danger posed by the variant. Informing an individual about a dangerous variant discovered during the course of research is a reasonable measure that an investigator can take to rescue that individual.[21]

Many participants would like to learn about secondary findings, as noted above. Consequently, returning secondary genomic findings demonstrates respect for the majority of participants' preferences and views. Advising potential participants in the informed-consent process that certain secondary findings will be returned also demonstrates respect for persons and allows those who strongly object to the receipt of secondary results to decline research participation. Additionally, returning clinically important findings demonstrates respect by providing participants with information they can use to make choices concerning their health and life plans. By extension, acting with respect and recognizing the contributions of participants will help to foster a stronger relationship between investigators and participants and promote trust. Trust in the research enterprise is

becoming increasingly important as the public realizes the potential utility of ES/GS data and researchers include more sequencing in their studies.

The principle of justice is also relevant, because individuals in similar situations should be treated similarly and fairly. The service proposed here can promote justice by ensuring equitable access to the possible benefits of information about actionable secondary genomic findings. As noted above, only a minority of researchers, typically those with the available resources to do so, are currently providing secondary findings to participants. In the absence of agreement about any ethically relevant distinctions among ES/GS research projects, or among research participants, acting in a way that allows more research projects to deliver equally important findings is an appropriate goal. Overall, it is desirable for the research enterprise to treat similar participants similarly rather than arbitrarily with regard to this benefit.

Potential Objections to the SGFS and Challenges to Be Addressed

Although we are optimistic that this proposal represents a net benefit to participants and to the research enterprise, several possible drawbacks are inherent within its structure and merit further consideration. One objection might be that researchers should allow participants more control over whether or not they receive secondary genetic results. In our proposal, participants would not routinely receive findings in genes outside of the pre-specified gene list or those judged to not be clinically important or actionable.[26] However, providing participants with information during the consent process about how secondary findings will be handled allows them to make a decision about participating in the research. If they do not agree with how findings will be returned, they can choose not to participate in the study. Many sequencing results will be of unknown significance, and the decision to provide participants only with clinically meaningful and actionable secondary findings from ES/GS research is driven more by beneficence than by autonomy. Some would argue, in agreement with clinical ES/GS recommendations,[27] that participants might wish to opt out of the secondary-findings analysis. However, it is important to recognize that opting out requires extensive knowledge on the part of the persons obtaining informed consent so that participants understand the potential significance of the information they might be forgoing, such as genetic information of potential life-saving value to themselves or their relatives. We propose that PIs and IRBs will need to determine whether this is appropriate for a given protocol. There is also the question of whether participants or investigators might pick and choose among the genes or disorders for which secondary-findings analysis could be performed. We suggest that, with current tools and resources, such customization is impractical (although this could change in the future). Therefore, with a defined gene list that has been vetted by institutional genetics experts, professional organizations, and an IRB available as a guide and arbiter, we find it justifiable to restrict research participants from choosing which particular variants or genes will be analyzed in their research dataset.

Another possible issue related to the proposed service is the potential obligation to re-contact former participants for updates on re-interpretations of variants detected long after the initial analysis has been completed. There has been discussion concerning the extent of this obligation in the context of both research and clinical care.[28] Although we acknowledge that re-contact could, in some cases, provide a substantial health benefit to research participants whose data had been evaluated by the service in the past, it is impractical to revisit every past participant's data whenever the gene list or the interpretation of variants is updated. At this time, for practical reasons of cost and logistics, we propose that this secondary interpretation activity be performed only once after the original research ES/GS data are generated. Further analyses would not be expected, although this issue should be revisited as experience is gained and in response to technologic advances. It is important that the investigators' intention to perform only a single analysis to detect secondary findings is clearly conveyed in the consent process.

Finally, the risks of losing confidentiality or privacy related to sharing genomic data, which are often cited as a concern in proposals to create inter-institution databases of genomic-variant information, must be carefully managed with state-of-the art security protections. Although there will always be risks related to increased handling, manipulation, transfer, and reporting of genomic data, these problems are not limited to the context of a SGFS, and we expect that the potential benefits of the service will outweigh potential risks to privacy and confidentiality.

Future Directions

We anticipate that the formation of this service will benefit participants by allowing them to receive information about clinically meaningful and actionable secondary genomic findings and that it will benefit researchers by addressing their obligations to participants and clarifying what is considered ethical conduct in the field of clinical genomics research. We believe that disclosure of meaningful secondary genomic findings would eventually become an expected norm. We caution that this is only an initial iteration of a solution to a critical need in pursuit of what we consider a worthwhile objective. A number of issues, such as cost management, unforeseen risks, participant acceptance and understanding of the limitations of the analyses performed, and the result-disclosure timeline associated with participation, will need to be studied and evaluated once this service is implemented. In addition, there is a theoretical concern that individuals might

engage in research studies in order to undergo opportunistic screening for secondary variants to address a need for clinically indicated testing. We fully expect that the SGFS would evolve substantially in response to research on these (and related) issues in clinical genomics.

We recognize that this service might further blur the gray area between the provision of clinical care and the conduct of clinical research because research protocols that use this service might provide participants with significant clinical benefits. Clearly distinguishing between the goals of clinical care and those of clinical research is thought to be essential for protecting the rights of patients and participants because it helps them understand the purpose of research and their potential to benefit directly from participation. We and others find the distinction between clinical care and clinical research to be increasingly strained in ES/GS research because such research simultaneously contributes to the furthering of general knowledge and the generation of individual findings that might have clinical relevance and utility. In other contexts, such as learning healthcare systems,[29] investigators have also begun to recognize and acknowledge that the ethics of research and clinical care overlap more than has often been recognized and that it might be appropriate to work toward reconciling and merging these activities in some settings.[30] Instead of trying to convince participants that they should not expect to benefit from participating in research, investigators should anticipate and accurately communicate potential clinical benefits in the consent process. At the same time, we acknowledge that many researchers are not yet (and some might never be) equipped to provide these clinical benefits in the context of their research protocols, given the fast pace at which genomic sequencing technology has progressed. Accordingly, the SGFS proposed here preserves the distinction between research and clinical roles by assigning responsibility for managing the clinically actionable aspects of the endeavor to experienced clinical genetics providers. This apportioning of responsibility helps to more clearly distinguish between the roles and interests of the research team (i.e., discovery of generalizable knowledge) from those of the clinicians, whose responsibility it is to provide care in the best interests of their patients.

A remaining challenge for the SGFS is how to apply this approach to research projects included in the secondary-findings service when the participants lack the resources to properly utilize its findings. For example, a participant who is from a resource-poor region where there are no healthcare services accessible to provide follow-up care might find it difficult to use findings provided by the SGFS. This situation presents a difficult dilemma for PIs and IRBs. On the one hand, it would seem to be unfair to bar such a person from participating in a study simply because he or she might not be able to access the resources needed to benefit from clinically actionable results. On the other hand, it might be inappropriate (and perhaps harmful) to return results that a participant cannot use or do something about. The participant might experience considerable worry and stress and feel abandoned by the researchers. We do not have a solution for this problem, and we encourage further discussion from relevant stakeholders.

In addition to the more immediate potential benefits and challenges described above, creation of a standardized process and service for the return of clinically actionable variants to research participants would permit research into the consequences of the return of such secondary findings. Because this SGFS would return a standardized set of variants in a consistent manner to participants across a wide spectrum of research projects, it can serve as a source of empirical data for evaluating the benefits or harms. We encourage researchers to adopt systematic approaches to secondary findings both for the benefit of individual participants and to facilitate improvement in research practices overall. This service, which we hope to implement in the multi-institute, multi-IRB environment of the NIH IRP, could serve as a template or model process for similar services in extramural institutions and will evolve as new genomic discoveries come to light.

Supplemental Data

Supplemental Data include two tables and can be found with this article online at http://dx.doi.org/10.1016/j.ajhg.2016.01.010.

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