Journal of Clinical and Translational Science

ACTS
ASSOCIATION FOR CLINICAL AND TRANSLATIONAL SCIENCE

TRANSLATIONAL RESEARCH, DESIGN AND ANALYSIS
RESEARCH ARTICLE

Informed consent for next-generation nucleotide sequencing studies: Aiding communication between participants and investigators

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Journal of Clinical and Translational Science (2017), 1, pp. 115–120 doi:10.1017/cts.2016.21

Introduction. Obtaining informed consent from prospective participants for research studies that include next-generation nucleotide sequencing (NGS) presents significant challenges because of the need to explain all the potential implications of participating, including the possible return of "incidental" findings, in easy-to-understand language.

Methods and Results. After reviewing the consent processes at other institutions, we decided to supplement the protocol-specific informed consent form with the following: (1) a short pamphlet for the prospective participant that includes a series of questions that she or he is encouraged to ask the investigator, and (2) a more detailed companion guide for investigators to help them develop simple-language answers to the questions. Both documents are available to use or modify.

Conclusions. We propose an approach to obtaining informed consent for NGS studies that encourages discussion of key issues without creating a complex, comprehensive document for participants; it also maximizes investigator flexibility. We also suggest mechanisms to return restricted information to participants.

Received 5 February 2016; Revised 8 April 2016; Accepted 10 November 2016; First published online 7 February 2017

Key words: Translational research, design and analysis, patient-centered research, genetic counseling.

Next-generation sequencing (NGS) of nucleic acids has revolutionized biomedical science and medical care. At the same time, it has generated bioethical questions of enormous complexity about which there are differing views, even among experts in the field. Thus, obtaining informed consent for participating in these studies is challenging, and attempts have been made to define core elements of consent specific to NGS studies to ensure that participants have all of the information that they need to make an informed decision about participating [1–4]. This report summarizes the results of a Rockefeller University working group charged with reviewing the current status of obtaining informed consent for NGS research studies and provides the documents developed by the working group to assist potential research participants and investigators conducting informed consent discussions with potential research participants.

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Background

Many institutions offer genetic diagnostic testing and genetic analysis of tumors as clinical laboratory tests designed to provide vital information that can inform medical decisions about a single patient [5]. In these circumstances, there is the potential for the patient to directly benefit from the NGS studies, providing a framework for weighing risks and benefits. In contrast, research studies that utilize NGS technology are usually primarily designed to obtain generalizable knowledge rather than provide specific information to guide therapy or interventions to prevent the development of, or ameliorate, the manifestation of disease [6]. As a result, often there is little or no expectation of direct benefit from participating, making the risk-to-benefit ratio more difficult to assess. Often, however, there is no clear separation between these different uses of the NGS technology, as it is increasingly common for NGS to be applied to rare or hard-to-treat diseases, where the goals of the research are simultaneously focused on both obtaining generalizable knowledge and identifying a genetic abnormality that may result in a new treatment for the disorder [7, 8]. Research performed on biobank samples has added complexity, as samples may be tested at some indeterminate time after donation, by investigators who may be independent from those who obtained the original consent [9–17].

Investigators at our institution perform studies across this entire spectrum, including studies in which there are no candidate genes on which to focus [18]. Moreover, although the early adopters of NGS for human studies tended to be investigators with strong backgrounds in human disease research and human genetics, the technology is increasingly being adopted by investigators with less expertise and experience in human subjects research and human genetics.

The Human Genomics Working Group (HGWG)

The above considerations led us to bring together a multidisciplinary group of individuals to discuss the broad range of scientific, technical, and bioethical issues raised by performing research studies using NGS. The group, titled The Human Genomics Working Group (HGWG), engaged a broad group of stakeholders including the leadership of the Rockefeller University Center for Clinical and Translational Science; investigators conducting human studies involving NGS; members of the Rockefeller University General Counsel's Office, Institutional Review Board, and Bioinformatics/Biostatistics group; genetic counselors at Rockefeller University and Sarah Lawrence University; and representatives from the New York Genome Center. The membership of the HGWG overlapped extensively with the membership of our Navigation program [19], which we created to assist investigators develop their human subject protocols by providing access to experts and resources in all aspects of human subjects research, including advice and training on optimizing the informed consent process.

The HGWG first met in July 2013 and has met periodically thereafter, with the goal of providing resources to support investigators who want to perform research involving NGS. Specifically, the group chose to focus on the development of policies, templates, resources, and best practices to assist investigators with the complex issues related to informed consent, bioethics, data security, privacy, and information technology involving the use of NGS in research.

To begin the process, the committee collected informed consent forms and related materials from investigators at institutions known for their excellence in conducting such studies, including the Dana Farber Cancer Center, the University of Pennsylvania, the National Institutes of Health, Baylor College of Medicine, Johns Hopkins School of Medicine, Washington University School of Medicine, and the University of Washington School of Medicine. This document collection was augmented by a comprehensive search for educational materials that could be used to assist research participants in understanding the full range of implications of their participation, as well as a compilation of legal regulations that govern such research. The role of genetic counselors in the process was explored in detail. Materials related to data storage, data security, and data sharing were also obtained.

Many of the group's deliberations focused on the return of information to research participants, particularly the return of "incidental" findings, using as point of departure the increasingly voluminous literature on this topic that appeared at approximately the same time [20–25]. Many other discussions dealt with the related topic of when studies should be conducted in laboratories certified for returning results of genetic tests to patients and their physicians for medical decision-making purposes under the federal Clinical Laboratory Improvement Act (CLIA) and the New York State Clinical Laboratory Evaluation Program (CLEP). In-depth interviews with investigators conducting NGS research provided insights into the range of their different research goals and the distinctive aspects of the populations studied, including language and geographic barriers. A theme carried across all the topics of deliberation was the need to support an informed consent process that would be flexible enough to accommodate the wide variation in medical and research literacy among research participants. Below, we summarize the major findings and recommendations of the HGWG.

Information for Potential Research Participants

After reviewing the current Rockefeller Institutional Review Board (IRB)-approved template for obtaining consent for participation in studies involving genetic testing, the HGWG concluded that it included all the fundamental information required, and that adding the details needed to explain the entire range of issues specifically related to NGS would make the consent unduly long and difficult to read and understand; it would inevitably also include information that was not specifically germane to the study for which consent was being obtained. As a result, the group concluded that the current template is clear about the general rights, protections, and risks associated with genetic studies, and that specific information about the risks and benefits of a particular study should be inserted in the consent form template on a protocol-by-protocol basis as judged best by the investigator and IRB.

The working group considered the wide range of medical literacy of the general public and the need for investigators to have the tools and skills to tailor the informed consent conversation to maximize comprehension. Initially, the HGWG sought to identify publicly available materials that would convey the essential genetic, biological, and medical concepts through a broadly accessible user-friendly platform. It was initially unable, however, to identify educational materials for potential research participants that delineated in simple language all of the important considerations relating to NGS research. As a result, the HGWG began to try to draft information specifically geared to the needs of potential research participants. After multiple attempts, it became clear that trying to create a single-tier platform to cover all the key aspects, as well as their implications, for a range of different groups of potential participants and their family members in simple language was too great a challenge. As a result, the HGWG shifted its emphasis from direct education of research participants to creation of complementary documents for both the potential participants and the investigators to support the consent process. The committee identified an excellent short trifold pamphlet developed by the New England Research Subject Advocacy Group in collaboration with community members entitled "Genetic Research" [26]. The pamphlet is written in simple language, and provides a valuable introduction to understanding research involving genetic studies. It ends with a series of questions for the potential participant to consider. The HGWG then modified a subset of the trifold pamphlet questions, and added additional questions to cover a broader range of topics (Table 1 and online Supplementary Material S1) and created a much more extensive companion document (Investigators Guide) to assist investigators in answering the questions included in the participant pamphlet (online Supplementary Material S2). Thus, the goal shifted from trying to produce a comprehensive document for potential participants to helping both potential participants and investigators prepare for the informed consent discussion before enrollment into the study by (1) providing potential participants with questions to ask, the answers to which will provide them with a comprehensive understanding of the potential benefits and risks of participating in the study; and (2) providing investigators with guidance and sample language to assist them in responding to the questions the participants have been encouraged to ask. To augment the materials developed by the HGWG, the group later identified several excellent generic genetic educational materials for nonscientists, although ones requiring relatively high literacy, including those provided on the Web sites of the Genetic Alliance (http://www.genesinlife.org/genetics-101/how-does-genetics-work) and the U.K. National Genetics and Genomics Education Center (https://www.genomicseducation.hee.nhs.uk/resources/online-genomics-resources). An excellent video describing NGS research in simple language was also identified (https://www.youtube.com/watch?v=IXamRS85hXU) [27]. The HGWG made links to these and other resources available on the Rockefeller University Web site, http://www.rockefeller.edu/ccts/resources, under the heading "Genetic Research Studies: Educational Materials for Participants and Investigators."

https://doi.org/10.1017/cts.2016.21 Published online by Cambridge University Press

Table 1. *Questions contained in the research participant pamphlet entitled "Genetic Research at The Rockefeller University Hospital and Center for Clinical and Translational Science"**

Questions to Ask
1. What is the purpose of the study?
2. Why perform a genetic analysis?
3. How will you collect my genetic samples?
4. What will you look for in my genetic information?
5. What type of genetic testing will be performed?
6. Will you also want to test members of my family?
7. How reliable is the genetic testing?
8. What happens if the tests reveal a medical issue?
9. What if you find something that you did not expect?
10. Will I receive results from this study? Will anyone else?
11. Will the test results become part of my medical record?
12. How do you protect the confidentiality and security of the information in the genetic material?
13. Will test results impact my health insurance coverage in the future?
14. Will my DNA sequencing data be shared with other researchers?
15. Will my samples be used for future research? If so, will I need to give my consent?
16. What impact might my participation in the study have on my family planning and on members of my family?

*"This material is the work of the New England Research Subject Advocacy Group and contributing partners (http://catalyst.harvard.edu/regulatory/language.pdf) with additions by The Rockefeller University supported by the Clinical and Translational Science Award program."

Information for Investigators

The Investigator's Guide is geared to the questions contained in the modified pamphlet, and contains model language for explaining to potential participants the basics of genetics and the core elements of informed consent, including the reasons for conducting the research and the procedures that will be performed, as well as the following more complex topics.

Incidental Findings

The most contentious issue in the literature concerns the return of information to research participants that was obtained by NGS, but was not the primary goal of the research. These "incidental" findings (which if actively sought are termed secondary findings) [28] are not related to the primary aim of the genetic testing [20–25]. Empirical data from two studies involving data on 1000 and 6503 participants [29, 30] indicate that incidental findings of potentially "actionable" medical significance as defined by the American College of Medical Genetics (ACMG) [3] are found in ~1.2%–3.4% of individuals, with individuals of European descent at the higher end and individuals of African descent at the lower end of the range. In contrast, the NIH Undiagnosed Diseases Program reported that 14 of the 159 families they studied (8.8%) had a reportable incidental variant, with the higher percentage perhaps reflecting both the relatively small number of participants and the population studied [31]. An analysis based on a novel web-based tool indicated that ~20% of more than 1000 genomes analyzed had a pathogenic variant that required further evaluation [32]. Hovering over the debate is the concern about false-positive findings due to erroneous annotations, sequencing error, incorrect penetrance estimates, and multiple hypothesis testing [33]. Although the first 3 of these sources of error are small and will become even smaller over time, the last presents theoretical concerns that can best be addressed by the participation of expert clinicians [33].

Two mutually inconsistent analogies have been put forward to support the differing views about obtaining and returning incidental findings. On the one hand, there is likely to be near-uniform consensus among physicians that a radiologist is duty bound to report an incidental bone lesion identified on the chest X-ray of a patient referred for evaluation of pneumonia. On the other hand, there is also likely to be near-uniform consensus among physicians that a clinical laboratory is not duty bound to perform additional tests on a serum sample sent for a specific diagnostic test, simply because it may uncover abnormalities that would lead to an early diagnosis of an unknown disease. Where the incidental findings found during NGS research fit in the above spectrum is arguable, but the consensus among the HGWG was that incidental findings that are "actionable"—that is, able to be translated into an action that may prevent or ameliorate disease—should in general be provided to the individual [3]. Empirical studies of the attitudes and preferences of the general public, including studies of under-represented minority patients and medical and research professionals, support the return of actionable incidental findings, although there is less agreement within and among these groups about whether investigators should be obligated to actively search for actionable incidental findings and whether participants should be allowed to opt out of receiving such potentially life-altering information [17, 28, 34–42]. Further complicating decision making is the realization that the causal connection between a variant and a disease may be less than definitive, leading groups such as the ACMG, the Association for Molecular Pathology and the Clinical Genome Resource (ClinGen) to provide a gradient scoring system (https://www.clinicalgenome.org/site/assets/files/2657/current_clinical_validity_classifications.pdf and http://www.ncbi.nlm.nih.gov/clinvar/docs/clinsig/) [43]. Even with the most advanced analyses, however, assessing whether a particular variant is likely to be deleterious can be challenging [44]. Thus, each study requires that the investigator and the IRB agree on the most appropriate way to address both the research needs of the project and the participant's best interests in receiving information about the results of the NGS.

The HGWG recognized that returning actionable incidental findings would increase the cost and complexity of studies in which the initial sequencing was not performed in accordance with CLIA or CLEP regulations, as it would require obtaining an additional sample and retesting by laboratories performing the tests in accord with these regulations. Moreover, this may be very difficult to achieve for participants who live in foreign countries with limited access to medical facilities. As the regulations for CLIA/CLEP certification of results for NGS studies become better defined and as more laboratories obtain certification, some of these obstacles may diminish.

Other aspects of the return of information also require consideration. For example, some of the actions that can be taken in countries with developed healthcare systems, such as serial colonoscopies, may not be routinely available in resource-limited countries. Thus, investigators who study participants from such countries need to consider how they can help participants gain access to such services. In addition, when no actionable findings are reported to participants, it is important that they do not fall prey to what we have termed the "diagnostic misconception" [45], whereby they assume that if they are not re-contacted by the investigator, then their genome must be free of any problematic variants.

As new correlations between genetic variants and disease states are being made at a rapid rate and it is predictable that this process will continue for an extended period, one of the thorniest policy issues in the return of incidental findings relates to the responsibility for providing updated analyses of actionable findings over time. If the bioethical obligation to provide actionable information to the participant is judged to be present at the beginning of the study, it is reasonable to conclude that it also persists throughout the research participant's life (and perhaps even beyond for findings of significance

https://doi.org/10.1017/cts.2016.21 Published online by Cambridge University Press

to the individuals' relatives). Fulfilling this obligation is particularly challenging for research studies of limited duration, or when an investigator may move to another institution, retire, or die. It also poses challenges related to logistics of tracking research participants essentially indefinitely while still protecting their privacy. The HGWG's consensus was to empower participants to decide if, and when, they want to have their genome re-evaluated for additional information by suggesting that investigators help participants who want ongoing information enter their DNA sequence into one of the internet-based services that provide medical interpretations such as My46 (https://www.my46.org). The research participants therefore "own" their sequences and have the option of requesting an updated analysis at any time in the future. The ClinGen clinical genome resource and the associated ClinVar database potentially offer an alternative method for individuals to obtain authoritative updated information on the medical implications of their DNA variants [46]. This approach would need to be coupled with an understanding in the initial consent of the potential limitations of the accuracy of the sequence if it was not obtained in accord with CLIA/CLEP standards, and thus the need for verification of variants if they are in the future judged actionable. Despite these challenges, there have been calls for self-guided management by participants of results of NGS over time, and models of consent that incorporate participant control over their data [47, 48]. Such an approach is likely to be crucial if individuals would like to receive information about variants that may be deleterious, but not actionable, as, for example, deleterious variants that may have an impact on family planning for the participant or another family member. The Coriell Institute for Medical Research has championed an approach to give participants access to their own data, if they choose to view it, through a Web portal that is periodically updated and that provides personalized risk reports and genetic variant results for potentially actionable conditions [49]. Rebecca Fisher [50], a breast cancer survivor and patient advocate who has eloquently described her frustration and sense of betrayal in not receiving timely information of great importance to her and her family after participating in a genetic research study, has argued persuasively for greater participation of research participants in setting policies related to the return of genetic information in research studies. We have developed validated methods for obtaining the perceptions of research participants regarding their participation, including a study of almost 5000 responses, in which one of the most consistent findings was participants' desire for the return of research results [51, 52]. As a result, we are coupling our initiative to educate potential participants and investigators with novel methods to obtain feedback from, and sustain communication with, research participants. This will provide longitudinal data on how participants feel about the completeness of the original NGS research study consent process as viewed from a long-term perspective.

Procedure to Assist the IRB in Deciding Whether to Approve a Request from an Investigator to Return Information in Addition to that Agreed to in the Original Informed Consent Document

The working group recognized that there may be circumstances in which it may be appropriate to return data outside of the information agreed to in the informed consent document and originally approved by the IRB. One hypothetical example is where new information recently obtained by an investigator links a genetic variant found in a participant to a disease for which one can take preventive measures to mitigate the medical impact of the disorder. To address such circumstances, the working group proposed the creation of a committee separate from, and advisory to, the IRB composed of individuals with expertise in human genetics, genetic counseling, bioethics, and regulatory issues that could rapidly evaluate requests from investigators who might like to share information with participants outside of what was approved by the IRB. The results of the committee's decision and the reasoning behind it would then be made available to the IRB for its final determination.

Although there have been a number of empirical studies on the preferences of research participants and the policies of institutions in returning NGS information to participants, the data are limited. Klitzman *et al.* [53] reported in their interviews with 28 genomics researchers and found wide variations in the way the investigators, their institutions' standing or ad hoc scientific review committees, and their IRBs dealt with the return of findings outside of the information agreed to in the initial informed consent. Yu *et al.* [54] reported on the results from a survey of 760 genetics professionals and found broad support for both offering to return actionable incidental findings and respect for individual preferences in the return of information, including information that may be of utility in family planning even if not immediately actionable. Bollinger *et al.* [55] reported on focus groups conducted with 89 members of the public, and concluded that on the whole they were eager to receive individual genetic research results as "a sense of ownership," especially when the results were potentially actionable, and that they felt it was the investigator's obligation to pay for the confirmation of the results if necessary. As IRBs often lack deep expertise in human genetics and genetic counseling, having an additional independent review committee composed of experts in genetics and genetic counseling can complement the final review by the IRB. National guidelines such as those proposed by the ACMG can be helpful, but will inevitably be incomplete in addressing all potential real-life scenarios and will lag behind the latest information. It seems prudent therefore to create a process that provides for an opportunity to deal with unanticipated issues on a case-by-case basis.

Conclusions

NGS has revolutionized genetic research, but has added complexity to obtaining informed consent and returning information to research participants. After reviewing the literature, including studies of research participants' views, and conducting extensive discussions with leading investigators from across the United States, we have developed a 2-pronged approach that involves both encouraging potential research participants to ask specific questions in the course of their informed consent discussions and providing information to investigators to assist them in addressing all the key elements in obtaining informed consent for NGS studies. We believe that this approach provides appropriate institutional guidance while preserving the flexibility for individual investigators to tailor their studies to meet their scientific goals and their research participants' expectations.

Acknowledgments

We dedicate this work to Erica Sanborn (M.S., C.G.C.) who cared deeply about participants involved in genetic research, who suggested that we undertake this initiative, and who contributed important insights and suggestions that were incorporated into the final document. We thank all the members of the Rockefeller University Human Genomics Core Working Group whose discussions and critiques led to the creation of the documents and the policies we have adopted.

We thank and acknowledge the New England Research Subject Advocacy Group and their member institutions' affiliated universities and academic healthcare centers for allowing us to modify the excellent pamphlet they developed for volunteers considering participating in genetic research protocols (Genetic Research; http://catalyst.harvard.edu/services/rsa). Their work was conducted with support from the National Center for Advancing Translational Sciences, National Institutes of Health, through Boston University Clinical and Translational Science Institute, under award number

1UL1TR001430; the Dartmouth Clinical and Translational Science Institute, under award number UL1TR001086; Harvard Catalyst | The Harvard Clinical and Translational Science Center, under award number 8UL1TR000170-05; Tufts Clinical and Translational Science Institute, under award number UL1TR001064; UMass Center for Clinical and Translational Science, under award number UL1-TR001453; and the Yale Center for Clinical Investigation, under award number UL1TR000142. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

Financial Support

This study was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, Clinical and Translational Science Award to Rockefeller University (UL1-TR000043 and UL1-TR001866).

Declaration of Interest

None.

Supplementary Material

To view supplementary material for this article, please visit https://doi.org/10.1017/cts.2016.21

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https://doi.org/10.1017/cts.2016.21 Published online by Cambridge University Press