SCIENCE AND SOCIETY

Research ethics and the challenge of whole-genome sequencing

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Abstract | The recent completion of the first two individual whole-genome sequences is a research milestone. As personal genome research advances, investigators and international research bodies must ensure ethical research conduct. We identify three major ethical considerations that have been implicated in whole-genome research: the return of research results to participants; the obligations, if any, that are owed to participants' relatives; and the future use of samples and data taken for whole-genome sequencing. Although the issues are not new, we discuss their implications for personal genomics and provide recommendations for appropriate management in the context of research involving individual whole-genome sequencing.

The recent publication of the first two individual human whole-genome sequences is significant not only because it symbolizes a tremendous stride forward in our technological and scientific ability to understand the genetic basis of disease, but because it provides a glimpse into the future of genomic medicine. James Watson[1] and Craig Venter[2] are the first of many whose genomes will be sequenced for research purposes and eventually as part of routine clinical care[3,4]. This creates a unique opportunity to reflect on the ethical, legal and social challenges that are associated with this next generation of personalized genomics. Privacy, confidentiality and the potential for subsequent discrimination have been identified as major considerations[5–7], but other issues remain for those such as Watson, Venter and nine of the 'Genome 10' (REF. 8) who have agreed to have their genomes mapped non-anonymously.

We have identified three major ethical considerations that must be addressed in research involving human whole-genome sequencing or the acquisition of large amounts of genome sequence data: the circumstances under which research results are disclosed to research participants; the obligations, if any, that are owed to participants' close genetic relatives; and the options regarding how future uses of samples and data taken for whole-genome sequencing are dealt with. Although all of these issues have been implicated in past genetic research and clinical practice, and may be resolved as genome sequencing takes on a more defined clinical role, at this nascent stage, individual whole-genome research intensifies their significance and the need for policy consideration. In many ways, the management of these ethical challenges can be simplified in the cases of Watson, Venter and the participants in the Harvard Personalized Genome Project because of the unique knowledge, expertise and sophistication of the research subjects[9]. However, these special circumstances will not apply to future projects, creating the need for general guidance on how best to manage these important ethical considerations.

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We propose specific recommendations for each of these ethically controversial issues, which can be used to guide research practice and stimulate policy development (BOX 1).

Reporting back research results

When James Watson received a miniature hard drive with his entire genome sequence, it was more than a mere symbolic gesture. Although Watson is a scientist with an individual and academic connection to the personal genome initiative, at that moment he was also a research participant receiving the raw data from a unique genetic research project.

Much has been written on when and how research participants should receive genetic research results[10–12]. Knoppers and colleagues suggest that the scope of the duty to disclose will vary depending on "the type of study, the clinical significance and reliability of the information, and whether the study involves patients, genetically 'at-risk' families for a tested predisposition or healthy volunteers."[13] Although these recommendations are informative, they were not crafted with whole-genome sequencing in mind, and in most jurisdictions there are still no definitive research ethics policies regarding the return of research results[14].

Research ethics norms remain in constant flux. Nevertheless, convincing arguments have been made for allowing research participants to be permitted access to their personal data if they so choose[12–15]. Given the degree to which a whole-genome sequence implicates individual integrity[16], there is little reason to suppose that these arguments would not apply to research participants in this context. Furthermore, as the media coverage intensifies[1,17], the commercial market for genome sequencing grows (for example, see the 23andMe web site) and direct-to-consumer marketing for genetic tests become more common[18], the desire for information and the expectations of research participants for receiving their results are likely to increase. As personal genome research moves forward, researchers should expect that research participants will begin to assert their right of access. However, several important ethical and policy issues regarding the form and process of disclosure

must be addressed before any transfer of genome data to research participants should occur.

First, what kind of data should be provided to research participants? Should participants simply be given their raw sequence data? For most individuals, this form will be meaningless. Participants are likely to want to learn more[19,20]. An annotated listing of potentially relevant genes would provide more information, but this level of analysis would require validation in an approved clinical laboratory (at least in the United States)[21]. Such a process would be expensive and, without the appropriate expertise, the results could be subject to misinterpretation. These concerns will be exacerbated if whole-genome sequencing is offered in the commercial or clinical context, where appropriate research protections might not be present. As such, at this early stage in the era of personal genomics, we propose the following: all human whole-genome sequencing initiatives should be conducted under a formal research protocol, and should include the development of a data return and counselling policy that can be evaluated by the relevant research ethics board (recommendation 1.1). The second major issue that deserves attention concerns the process of disclosure and follow-up clinical care. The volume, complexity and clinical uncertainty of data generated in whole-genome sequencing will make the communication of research results tremendously challenging. Inevitably, the significance of the generated data will vary — from clearly clinically relevant (for example, monogenetic disease information), to potentially relevant (for example, risk information), to data of unknown clinical significance. Expertise is needed for interpretation and to ensure an adequate understanding of the health and social implications of the identified genetic variation, both in the present and in the future. At present, there is no standard mechanism for disclosing research results, and there are an inadequate number of physicians who are specially trained to interpret and communicate this information and to provide follow-up information and clinical care when new research findings are reported[22,23]. This suggests an expanded role for geneticists and genetic counsellors, as well as physicians; we therefore recommend that further training for primary-care physicians in genomics should be provided to facilitate the communication of research results, and to provide follow-up information and clinical care as new research findings are reported (recommendation 1.2).

Box 1 | **Summary of recommendations**

Returning research results

Recommendation 1.1. All human whole-genome sequencing initiatives should be conducted under a formal research protocol, and ought to include the development of a data return and counselling policy that can be evaluated by the relevant research ethics board.

Recommendation 1.2. Further training for physicians should be provided to facilitate the communication of research results, and to provide follow-up information and clinical care as new research findings are reported.

Recommendation 1.3. Only validated data of known clinical relevance should be integrated into the health record. Practice guidelines should be developed for determining what constitutes validated and clinically relevant data. A process should be developed to update an individual's health record with additional genetic information as research progresses and new knowledge about the clinical relevance of specific gene loci is gained.

Obligations to third-party relatives

Recommendation 2.1. During the initial informed consent process, investigators conducting human whole-genome sequencing research should discuss implications for family members and encourage participants to include close genetic relatives in decisions about research participation. As long as the risks associated with participation in genetic research can be minimized by ensuring professional integrity, maintaining confidentiality and implementing security measures to prevent unauthorized access to the data, additional informed consent from close genetic relatives should not be required.

Recommendation 2.2. In the context of data release, participants should be encouraged to notify affected family members, and investigators should take a family-centered approach to informed consent. The obligation to include at-risk relatives increases with the degree of relatedness to the primary research subject and, when inclusion is not practical, investigators ought to strongly encourage the research participant to discuss the research with his or her relatives and make a family decision about data release. The investigator should offer to help facilitate this discussion and should provide genetic counselling when appropriate. Objections from family members should be investigated by a research ethics consultation team, if available, and reviewed by the relevant ethics review board.

Recommendation 2.3. American Society of Human Genetics guidance regarding unauthorized disclosure of genetic risk to third-party relatives in the clinical context should be expanded to the research setting. As long as the data are validated, the permissibility of unauthorized disclosure will depend on the clinical relevance of the information and the potential to avert or alleviate known health risks.

Future uses

Recommendation 3.1. Policy work should focus on developing consent mechanisms that can be reconciled with existing consent norms, including the analysis of the appropriateness of a broad future-use consent model. In the meantime, genome researchers must ensure that research remains within the spirit of the original consent, or re-consenting should be considered.

Furthermore, genetic results of uncertain clinical validity will nevertheless generate potential concern about disease risk among otherwise healthy individuals. This concern may potentially lead to increased demand for more invasive follow-up diagnostics such as magnetic resonance imaging (MRI) or computed tomography (CT) scans, raising questions about who should pay for such services, and placing pressure on already stressed clinical providers. Even if wealthy individuals choose to pay for themselves, issues of justice and equity arise as personal genome sequencing will consume limited resources such as scanner, technician and physician time. Before whole-genome sequencing is integrated into routine clinical care, the potential effects on an already strained health-care system must be carefully considered[3,4].

Finally, if research participants are given access to genetic data of variable present and future clinical significance, the storage of that information and its integration into the health record must be carefully considered. There are several groups that are actively working on developing policy regarding the integration of genetic and genomic information into the electronic health record[24]. This work should continue, and those involved must think progressively and preventively about data generated from human whole-genome sequencing. It is recognized that a process of determining what constitutes validated and clinically relevant data will be difficult to implement. However, national advisory committees, such as the US Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS), can provide useful guidance

and set standards for determining what the terms 'validated' and 'clinically relevant' mean. Whole-genome sequence data should not be integrated into the health record until such detailed guidance, appropriate security measures and comprehensive policies are developed and ensured[25,26]. Of course, individuals retain the right to refuse genetic testing and can request that individual research results are not included in their health record. We therefore make several recommendations: only validated data of known clinical relevance should be included in the health record; practice guidelines should be outlined for determining what constitutes validated and clinically relevant data; and a process should be developed to update an individual's health record with additional genetic information as research progresses and as new knowledge about the clinical relevance of specific gene loci is gained[15] (recommendation 1.3).

Obligations to close genetic relatives

Data obtained from genome sequencing reveal information not only about the individual who is the source of the DNA, but also probabilistic information about the DNA sequence of close genetic relatives. This makes it possible to identify an individual by matching his or her DNA to the sequence of a relative's DNA[27]. The generation of whole-genome data significantly increases the ability to match the DNA of close relatives, and to reveal predictive information about relatives' present and future health risks. This raises important questions about what obligations, if any, are owed to the family members of individuals who consent to have their genome sequenced as part of a research protocol.

There are typically three activities associated with genomic research that can trigger questions about obligations to third-party relatives: initial consent for research participation, data release and data analysis. Third-party relatives are not generally considered to be research subjects of a particular study, so their consent is not required for an individual to participate in genetic research. In the United States, federal regulations define a human research subject as "…an individual about whom the investigator … obtains data through intervention or interaction with the individual, or identifiable private information."[28] As there is no direct interaction with third-party relatives, the central question is whether, in the course of sequencing an individual's genome, scientists are simultaneously obtaining identifiable private information about that person's close genetic relatives[29–31]. It is generally accepted that, unless the third-party relative is 'readily identifiable' (as distinguished from 'potentially identifiable'), he or she should not be treated as a research subject[32]. Of course, the identifiability of third-party family members is a matter of degree, and as technology advances someone who is only potentially identifiable today may become readily identifiable in just a few years.

> "…the secondary use of samples and data pose not only privacy and confidentiality issues … but also potential threats to the autonomy of individual research subjects and groups"

Because identifiability and the associated risks vary over time, it is more appropriate to conceptualize the obligations to third-party relatives as falling along a continuum. Ultimately, the probability of, and risks associated with, identification must be balanced against the scientific and clinical usefulness of the data and the autonomy-based rights of individuals to participate in genetic research without interference from more risk-adverse family members[33–35]. As the risks to relatives increase, the ethical obligations towards them intensify.

At the point of initial informed consent for research participation, the individual research subject is providing his or her autonomy-based consent to sequence his or her genome. Applying traditional bioethics and health law principles, the individual research participant's consent is both necessary and sufficient. Although this research activity may generate information about third parties that must be protected, it seems an inappropriate stretch of autonomy-based consent principles to say that they have a right to deny its use. Following this logic, we propose that during the initial informed consent process, investigators conducting human whole-genome sequencing research should discuss the implications for family members and encourage participants to include close genetic relatives in decisions about research participation. As long as the risks associated with participation in genetic research can be minimized by ensuring professional integrity, maintaining confidentiality and implementing security measures to prevent unauthorized access to the data, additional informed consent from close genetic relatives should not be required (recommendation 2.1).

In the context of data release, there is an emerging ethical consensus that researchers have greater obligations to address the concerns and protect the privacy of relatives when information on family history is published[33,34,36]. This is analogous to the public release of genomic sequence data. In both cases, privacy becomes more difficult to manage because of the widespread distribution of the information. Decisions about data release, an emerging policy norm[31,37], should therefore ideally include family members whose privacy is most at risk. However, it can be difficult to include third-party relatives in the decision-making process if they are unknown to the investigators or if the family dynamics are less than perfect. We therefore propose the following: participants should be encouraged to notify affected family members, and investigators should take a family-centered approach to informed consent (an approach that has already been embraced in many research ethics guidelines)[38]. The obligation to include at-risk relatives increases with the degree of relatedness to the primary research subject and, when inclusion is not practical, investigators should strongly encourage the research participant to discuss the research with his or her relatives and make a family decision about data release. The investigator should offer to help to facilitate this discussion and provide genetic counselling when appropriate. Objections from family members should be investigated by a research ethics consultation team, if available, and should also be reviewed by the relevant ethics review board (recommendation 2.2). Clinically relevant diagnostic and predictive information about family members' health risks can be revealed during the course of data analysis. There is extensive literature on the obligation to warn at-risk family members of genetic risk[39,40]. Although there is no legal consensus in the United States[41,42], ethically, the American Society of Human Genetics (ASHG) suggests that the unauthorized disclosure of genetic risk is permitted only if "attempts to encourage disclosure on the part of the patient have failed, the harm is highly likely to occur and is serious, imminent and foreseeable, the at-risk relative(s) is identifiable and the disease is preventable, treatable or medically accepted standards indicate that early monitoring will reduce the genetic risk."[32] These same general principles apply in the research context[43]. We recommend that the ASHG guidance regarding unauthorized disclosure of genetic risk to third-party relatives in the clinical context should be expanded to the research setting. As long as

the data are validated, the permissibility of unauthorized disclosure will depend on the clinical relevance of the information and the potential to avert or alleviate known health risks (recommendation 2.3).

Future uses of samples and data

Secondary uses of samples and data from genetic studies are common, but the informed consent processes that are used in the original collection of these samples have often not predicted their future uses in research. Often, no mention of secondary uses was made, or 'blanket consent' to any research use was obtained. The proliferation of electronic databases for genetic and associated information[37,44] and the international commitment to broad data sharing in genomic research[45,46] have made blanket consent increasingly desirable. However, the many possible uses for this information increases as whole-genome sequencing becomes more widespread, creating the potential for research to be conducted that is far outside the scope of the research for which the samples were originally collected. This heightens the legal and ethical issues that are already associated with the use of a blanket consent approach in other contexts[47,48].

Indeed, the secondary use of samples and data pose not only privacy and confidentiality issues, as discussed above, but also potential threats to the autonomy of individual research subjects and groups[49]. Individuals who willingly gave samples for the purpose of studying a disease of interest might be at risk of having their sample used to study other phenotypes, such as personality traits, IQ, behaviour or evolution and natural selection. As whole-genome sequencing becomes more common, these data become much more amenable to the study of complex traits. Although the study of other phenotypes might potentially be more useful to the research community, some might be less acceptable to the research subjects.

Although there is a long history of using biological material for research beyond the scope of the original study for which it was collected[50], the practice of broad data sharing in publicly accessible electronic databases emerged in the context of large-scale sequencing studies, such as the National Human Genome Project (USA) and the International HapMap Project. For these studies, unrestricted data release was essential because the primary purpose of the research was to create a reference genome or catalogue of genetic variation that was easily accessible and freely available to use for a host of other research purposes. In the early years of human whole-genome sequencing, the goals are similar: to advance technology and increase our understanding of genetic variation in humans. Thus, there are rationales supporting the position that individual human whole-genomes sequenced in the context of federally funded research ought to require consent for broad data sharing and unspecified research uses. However, such an approach might challenge traditional ideas of informed consent, which, in general, require that consent is obtained for each study that links to identifiable information. Can a person consent to something that they have no details about? This tension between the desire to support research in the public good and the need to protect individual rights and established ethics norms has become a major policy issue in other domains, particularly biobanking[51–53].

Given the importance of consent in research ethics, resolving this and other consent dilemmas (such as the scope of the right to withdraw) seems essential for the future of this work. Indeed, as the field advances and personal genomes are generated in the context of disease-association studies (for which the primary goal is to study a particular disorder(s)) and as more complete genomic data can increasingly be used to make inferences about a wide range of other traits (including non-disease traits), the challenges associated with consent seem likely to intensify. At a minimum, individuals ought to be able to participate in a particular genome-wide association study without having to consent to more extensive data sharing or broader research use.

For existing samples, data sharing and future use must be consistent with the original informed consent. Databases will need to be designed to restrict certain uses for which there is no consent, and secondary users must exercise professional integrity by ensuring that their research does not go beyond the scope of the participant's original consent. In some circumstances in which the participant has agreed to re-contact, re-consent might be warranted. Therefore, policy work should focus on developing consent mechanisms that can be reconciled with existing consent norms, including the analysis of the appropriateness of a broad future-use consent model. In the meantime, genome researchers must ensure that research remains within the spirit of the original informed consent, or re-consenting should be considered (recommendation 3.1).

Looking forward

As the cost of human whole-genome sequencing decreases, important questions will arise about whether this technology should be generally available, and if and how it should be integrated into routine clinical care[3,4]. Concerns about privacy and the complexities of informed consent will persist and intensify. Economic issues will relate to who will have access to the benefits of personal genomics, and whether public and private health-care systems will pay for the generation of an individual genome, follow-up clinical care or recommended preventive treatment to decrease genetic risk. We need to better understand, through empirical study, what the effects of data sharing are on research subjects, what types of use are acceptable and how to best determine, communicate and respect subjects' wishes about the use of the samples and data. Such studies should start on a small scale before moving towards a wide availability of data on a large scale. We are currently able to generate an enormous amount of genomic data, but we have relatively little appreciation for its function or significance. As a better understanding of the contribution of genetic variation to human diversity develops, more challenging questions will come to the fore; for example, questions about personal identity, the limits of genetic determinism and the value in human diversity. This is an exciting time for the field of genomic science; however, it is essential that, as we move forward, we do so with some caution and with conscious consideration, critical reflection and careful study of the many ethical and social implications of new developments at each step along the way.

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FURTHER INFORMATION

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23andMe: https://www.23andme.com
National Human Genome Project: http://www.genome.gov/10001772
International HapMap Project: http://www.hapmap.org
US Secretary's Advisory Committee on Genetics, Health, and Society: http://www4.od.nih.gov/oba/sacghs.htm

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