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## Personal genome research: what should the participant be told?

Amy L. McGuire<sup>1</sup> and James R. Lupski<sup>2</sup>

<sup>1</sup>Center for Medical Ethics and Health Policy, Baylor College of Medicine, One Baylor Plaza, BCM420 Houston, Texas 77030, USA

<sup>2</sup>Department of Molecular and Human Genetics and Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, One Baylor Plaza, BCM225 Houston, Texas 77030, USA

### Abstract

Should the results of whole genome sequencing research be disclosed to participants, in particular when the results have uncertain or indeterminate phenotypic consequences? This controversial question is considered in light of one author's (JL) experience as a geneticist who recently had his own genome sequenced.

### Current practice and policy

One of the most pressing ethical challenges associated with whole genome sequencing (WGS) research is what to communicate to study participants? Scientists can now generate whole genome sequence data at relatively low cost (~\$ 5000) [1], but analyses and interpretation of these data have proven more challenging than some may have anticipated. WGS will certainly reveal genetic variants with known clinical significance; however, most genetic variants discovered during the course of whole genome research will have uncertain or indeterminate phenotypic consequences\*. There are also interpretive limitations related to the sheer volume of data generated, the fluid nature of existing knowledge, and the lack of reliable reference datasets. Given these limitations, what information, if any, about genetic variants discovered during the course of WGS research ought to be disclosed to study participants?

Several well-known scientists have been among the first to participate in WGS research [2-4]. Perhaps because of their sophisticated understanding of genetics [2] and their unique relationship to the investigators (in some cases they were the investigators [3,4]), these subjects have been given access not only to clinically significant findings but to all of the data analyzed during the course of the research. This practice is consistent with recent social science studies that have found that most participants in genetic research wish to receive results, they see the communication of results to be a benefit of participation, and they report that they would be more likely to participate in genetic research if results were returned [5,6]. It is also consistent with international policies that recognize a right to receive results. As Knoppers and colleagues point out, "at the international level there may be an emerging ethical 'imperative' to return

Corresponding author: McGuire, A.L. (amcguire@bcm.edu).

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\*Some distinguish clinically significant findings discovered during the course of research that are beyond the aims of the study (incidental findings) from potentially significant findings related to the primary variables under study (research results). However, in WGS research this distinction often becomes blurred as the primary variables under study can be vague or ill-defined. In this paper, we use the terms 'research results' and 'research findings' interchangeably to capture the broad range of information discovered during the course of WGS research.

results in genetic research” [7]. However, it is inconsistent with US guidelines that suggest that only valid results that are known to be clinically significant and actionable be disclosed to study participants [8,9].

An understanding of the functional consequences of genetic variation is evolving; nevertheless it has expanded considerably over the past several years and is anticipated to continue to grow exponentially. This has led to the creation of an industry where consumers can access both clinically relevant genetic test information as well as results with unproven significance without the involvement of a health care provider (<http://www.dnapolicy.org/resources/DTCcompanieslist.pdf>). It has also led some to question whether research participants ought to have similarly broad access to their genetic information.

There are both risks and benefits to the disclosure of genetic variants discovered during the course of research. In this article we discuss these and consider them in light of the personal experience of one of the authors (JL), a geneticist who recently had his own genome sequenced as part of a research protocol (hereinafter “JL WGS”) [4].

## Ethical, practical and scientific considerations

Ethical considerations that are invoked to support broad disclosure of genetic research findings include: (i) individuals have a right to receive information about themselves; (ii) communicating genetic findings can benefit participants either because the information leads to positive health outcomes or because it provides them with some personal meaning; (iii) disclosure will increase trust in researchers and the research enterprise, ultimately leading to greater participation; (iii) subjects voluntarily agree to contribute to research and so the principle of reciprocity demands that they receive access to the knowledge gained and discoveries gleaned from such research; and (e) returning results is a sign of respect, which is a core ethical commitment in research. There are also scientific reasons to disclose genetic research results to study participants because it might facilitate recruitment into future genotype-driven studies [10].

From a participant's perspective, being informed of the results of research efforts can help satisfy their need to know more about their disease process, which might be the very reason they initially elected to participate. This understanding can provide an important benefit to participants, which might not be either anticipated or vicariously experienced by the researchers themselves. For example, in the JL WGS, although recessive inheritance of Charcot-Marie-Tooth disease was anticipated prior to WGS, potential dominant susceptibility to axonal neuropathy or carpal tunnel syndrome with heterozygous alleles at this recessive locus was not [4]. Furthermore, not only was the specific genetic etiology of the disease process revealed, but the ‘personalized medicine’ molecular and cell biological bases are now understood because of the WGS. These findings are scientifically important, but they also provided personally relevant novel insights into the disease process, which was viewed as a benefit to the participant (JL) and his family.

However, there remain many challenges to the communication of genetic research findings. Ethically, objections to the return of results are largely beneficence-based, focusing on the distinction between research and clinical care. It is important to avoid the ‘therapeutic misconception’ or mistaken assumption that the primary purpose of biomedical research is to benefit the individual subject because it could lead some to overestimate the clinical significance of research findings [11]. There is also concern that the disclosure of results with unproven significance will cause harm to participants by creating stress and anxiety. Most participants do not have as sophisticated an understanding of genetics as a practicing medical geneticist and so the disclosure of genetic findings might be overwhelming and/or meaningless. Finally, there is a danger that it could lead to a cascade effect [12], where potentially harmful

and unnecessary follow-up tests and procedures are performed on the basis of misinterpreted results or findings with indeterminate significance [13].

Legally, to ensure quality laboratory testing, The Centers for Medicare and Medicaid Services (CMS) (<http://www.cms.hhs.gov/>) regulates all laboratory testing performed on humans in the United States through the Clinical Laboratory Improvement Amendments (CLIA) [14]. Most research laboratories are not CLIA certified as they are exempt from the regulations as long as they do not report patient-specific information. In order to report results, either the research lab that analyses and interprets the experimental data must obtain CLIA certification or the results must be validated in a CLIA-certified laboratory. This can be expensive and should be built into the research design and budget.

There are also many practical challenges associated with the return of genetic research results. Particularly in WGS research, substantial amounts of data are generated, making it difficult if not impossible to manually annotate for each subject. Several groups have attempted to address this by developing automated systems that can facilitate the return of results [15]. These systems make it more feasible to return results but they cannot eliminate all of the practical hurdles associated with the disclosure of genetic findings discovered during the course of research, including downstream research conducted by investigators who access the data via a de-identified central repository, such as the database for genotypes and phenotypes (dbGaP) maintained by the National Institutes of Health (NIH).

Finally, there are scientific challenges to the return of results. Methods to generate raw sequence information are still evolving as are the software programs to analyze such data. Each sequencing method has its own error rates and these are not necessarily robustly quantified at this time. Standards for independent confirmation of putative significant variants have not been established. The massive amount of information, often >100 gigabases of sequence with each personal genome, in and of itself provides new challenges for quality assurance, data handling and storage. Data analysis requires computational interfaces with human mutation databases, the veracity of which cannot be assured. This latter point can lead to erroneous interpretation and telling a subject he/she either has or might develop the condition identified by the database search when the original database entry was based on data that were interpreted incorrectly. For example, in the JL WGS a variant was identified that in the human mutation database was associated with a clinically characterized 'persistent vegetative state' in a child, yet the subject did not manifest such clinical findings. Such a computational matching and database interpretation is further complicated by the fact that the actual penetrance of reported disease-associated variants in the 'unaffected populations' is completely unknown. These experimental and interpretive limitations are compounded by our ignorance of function of >90% of annotated genes in the human genome, not to mention the 98% of the human genome that is non-coding and for which we do not have a 'genomic code' equivalent to the genetic code to help decipher the potential significance and meaning of variations.

## Concluding remarks

These scientific and evolving knowledge limitations and the ethical challenges they raise must be weighed against the moral arguments in favor of returning results and the potential good that might be obtained through new knowledge. At this early stage of WGS research there should not be a moral or legal obligation to return results with unproven significance. At the same time, access to that information should not be prohibited, as long as someone with the necessary expertise is available to communicate the findings, as well as the limitations discussed above in a way that the participant can understand, and the participant determines that the potential benefits of receiving the research results outweigh the harms. Individuals, both investigators and subjects, will vary in their judgments on this issue. From the perspective

of someone who has been both an investigator and a subject (JL), overcoming the fear of the unknown can lead to scientific and self-discovery and can be an important step on the road to personalized genomic medicine.

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