RESEARCH LETTER

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Empirical Research on the Ethics of Genomic Research

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TO THE EDITOR:

Genome-wide research that explores the genetic basis of a specific phenotype has the potential to incidentally uncover data relating to other existing and potential future phenotypes. It is vitally important to explore the ethical implications of these technologies and understand how research participants, lay members of the public, genomic researchers and health professionals wish to utilize this new information. We describe a new study to gather large-scale empirical data on what genetic results should be shared with research participants taking part in whole genome research.

Whole genome studies, by virtue of involving all 20,000+ genes, inevitably produce large volumes of genetic data some of which will be of actual or potential clinical significance. Whilst some of this data will be directly "pertinent" to the phenotype under study (e.g., a child's developmental disorder), others are likely to be "incidental" in that they are completely unrelated to the phenotype being investigated. What should be done with this data and what might research participants want to know? A systematic review of research about these very issues revealed a "lack of relevant studies" and an "urgent need for empirical investigations in the disclosure or non-disclosure of genetic incidental findings" [Jackson et al., 2012].

The Deciphering Developmental Disorders (DDD) project is using genome-wide approaches to investigate ~12,000 children with severe undiagnosed developmental disorders. Research samples from probands and their parents are being collected from every Regional Genetics Service in the UK and Republic of Ireland [Firth and Wright, 2011]. Samples are sent to the Wellcome Trust Sanger Institute where high-resolution genomic techniques including array-CGH and exome sequencing are being used to identify genetic causes for such developmental disorders. Results that are likely to be etiologically relevant and pertinent to the child's phenotype are shared with the clinical center; incidental findings are not shared.

There is evidence to suggest that research participants in genetics studies want to receive pertinent findings relating to the medical condition under study [Wendler and Emanuel, 2002]. However, little is known about what research participants think about incidental findings, including clinically significant information relating to medical conditions *unrelated* to the disorder under study. There is much discussion in the medical, ethics, genetics and social sciences literature about the merits and pitfalls of sharing genomic information in a research and clinical setting [Kohane et al., 2006; Renegar et al., 2006; Knoppers and Laberge, 2009; Green et al., 2013] and increasing support for the position that it is ethical to share incidental findings from whole genome studies [Knoppers et al., 2006; Wolf et al., 2008; Beskow and Burke, 2010; McGuire and Lupski, 2010; Daack-Hirsch et al., 2011; Evans and Rothschild, 2012]. "Even pure scientists can and should advance research subjects well-being and respect their autonomy by making appropriate disclosures of potentially significant incidental findings" [Miller et al., 2008b]. In a clinical setting the American College of Medical Genetics has recently advocated the sharing of a predetermined set of incidental findings for each exome/genome sequence done [Green et al., 2013].

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[1]There is no universally accepted definition of what an incidental finding is [Wolf et al.,] and broadly speaking this could include variants of known and unknown clinical significance, variants linked to highly penetrant, serious, life-threatening conditions, non-paternity or ancestry data. For the purposes of our study, we have adopted a pragmatic distinction between 'pertinent' and 'incidental' findings as set out in this text. Whilst in the US definitions of incidental findings are becoming accepted in practice [Green et al.,] it is still not known how and whether these also apply elsewhere around the world.

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Empirical data on the attitudes, values and beliefs of research participants about receiving the results from *genomic* (as opposed to single gene) studies is limited. There have been several small-scale qualitative interview studies [Miller et al., 2008a; Meacham et al., 2010; Miller et al., 2010; Daack-Hirsch et al., 2011; Bollinger et al., 2012] as well as discussion about the feedback of genomic results within the context of biobanks [Johnson et al., 2012] and an evaluation of the attitudes of genetic health professionals [Lohn et al., 2012]. Such research has emphasized the need for further and larger scale studies in this area. Although much has been written about incidental findings in medical imaging, to our knowledge, there are no large-scale (n = 1,000+) mixed-methods studies that clearly demonstrate attitudes towards sharing of genomic incidental findings within a research or clinical setting.

To address this gap, we have designed a questionnaire and interview study to ascertain the views of families recruited to the DDD project, genomic researchers, genetic health professionals, laboratory staff and members of the public; as the questionnaire is online it is not limited by geography and thus people participating may be from anywhere in the world. The questionnaire is available at http://www.genomethics.org; film and animation are used to explain the concepts needed to answer the questions. We invite anyone interested in genomic research to complete it, and will be approaching 25,000+ people as part of our recruitment strategy. Research participants can indicate on the questionnaire if they are willing to be interviewed and we aim to interview 50–100 participants from the UK to explore their views qualitatively in more depth. The questions focus primarily on attitudes towards sharing incidental findings, how such findings could be categorized, what to do with findings of unknown significance, attitudes towards mining specifically for certain types of incidental findings as well as views on consenting procedures appropriate for whole genome studies. The questionnaire has been extensively piloted and UK Research Ethics Committee approval has been granted for this work (Ref: 11/EE/0313).

This social sciences research has been deliberately structured so that it is of relevance to all genomic research and not just those projects involving developmental disorders. Our ethics researchers are fully integrated into the team of genomic researchers at the Wellcome Trust Sanger Institute in Cambridge, UK and thus in a strong position to be able to explore the ethical issues relating to genomic research from the inside. The aim of this project is to contribute new empirical data that can be used in future policy making on the sharing of genomic data in a research setting. This will undoubtedly have direct relevance to the use of genomic technology in clinical practice.

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