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Return of results from genomic sequencing: A policy discussion of secondary findings for cancer predisposition

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ABSTRACT

Advances in DNA sequencing technology now allow for the rapid genome-wide identification of inherited and acquired genetic variants including those that have been identified as pathogenic alleles for a number of diseases including cancer. Whole genome and exome sequencing are increasingly becoming a part of both clinical practice and research studies. In 2013 the American College of Medical Genetics and Genomics (ACMG) recommended that results of pathogenic genetic variants in 56 genes, nearly half of which comprise cancer genes (including *BRCA1*, *BRCA2*, *TP53*, *MLH1*, *MLH2*, *MSH6*, *PMS2*, and *APC*), be returned to patients who have their genome sequenced independent of the purpose for the test. This recommendation has been highly controversial for several reasons, particularly the recommendation that individuals be returned secondary findings of disease causing variants for adult onset conditions regardless of age and without consideration of patient preferences. In addition, the policy regarding returning results of secondary findings from genomic sequencing studies in research settings is currently unclear. In response to these emerging ethical issues, the Washington University Brown School of Social Work in St. Louis, MO, United States hosted a policy forum entitled "*First do no harm: Genetic privacy in the age of genomic sequencing*" on February 25th, 2014. The forum included a panel of experts to discuss their views on ethical issues related to return of results in both the clinical and research settings. In this report, we highlight key issues related to return of results from genome sequencing tests that emerged during the forum.

Introduction

The completion of the human genome sequence in 2003 [1] has been followed by rapid advances in genomic technology and subsequent exponential increases in knowledge of human genetic variation, including that associated with both Mendelian and non-Mendelian diseases. Plummeting costs of genome sequencing technology [2] make it increasingly feasible to rapidly scan the whole genome (both genic and non-genic DNA sequence) and exome (genic DNA sequence) for inherited variants including those that have been previously identified or suspected as pathogenic alleles for cancer. Genome-wide genetic testing offers the potential to identify high risk populations for cancer prevention and control, which could ultimately lead to reductions in cancer morbidity and mortality. As a consequence, there has been intense interest in developing guidelines for returning results of pathogenic variants that are detected in genome sequencing tests for diseases, including cancer, for which prevention and/or early intervention is possible.

In March 2013, the American College of Medical Genetics and Genomics (ACMG), an organization that supports the medical genetics profession, published recommendations for reporting what was termed "incidental findings" of pathogenic variants detected in genomic sequencing tests [3]. The ACMG recommended that pathogenic or presumed pathogenic variants in 56 genes be reported to individuals who have their genome sequenced. The report defined incidental findings as "the results of a deliberate search for pathogenic or likely pathogenic alterations in genes that are not apparently relevant to a diagnostic indication for which the sequencing test was ordered" [3]. However, on the basis of a definition published by the U.S. Presidential Commission *for the* Study of Bioethical Issues, we use the term "secondary findings" throughout the manuscript in lieu of "incidental findings" to describe the active search for variants in genes recommended by the ACMG [4]. The genes were selected by the committee on the basis of their medical actionability. Nearly half of the recommended genes are

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well-known cancer susceptibility genes including: *BRCA1*, *BRCA2*, *TP53*, *STK11*, *MLH1*, *MLH2*, *MSH6*, *PMS2*, *APC*, *MUTYH*, *VHL*, *MEN1*, *RET*, *PTEN*, *RB1*, *TSC1*, *TSC2*, *WT1*, and *NF2*. The ACMG recommendation has been highly controversial, in particular the recommendation that results be returned to parents/legal guardians of children for pathogenic variants in genes associated with adult onset conditions. In addition, the lack of patient autonomy over whether to receive secondary findings in their clinical sequencing data has also been a subject of intense debate [5,6].

In response to these emerging policy issues, on February 25th, 2014, Washington University in St. Louis, MO, United States hosted a 90 min policy forum entitled "*First do no harm: Genetic privacy in the age of genomic sequencing*" that featured a panel of experts concerned about ethical issues associated with genomic sequencing (panelist biographies are provided in the Appendix). We note that the debate generated by the ACMG report is not specific to the U.S. [7,8] nor is it the only position articulated in the U.S., but the forum mainly focused on this report as a starting point for the policy conversation. The 90 min policy forum format allowed for considerable audience discussion following each 4–7 min panelist presentation on return of results in both clinical and research settings (video is available upon request). In this report, we discuss key issues regarding return of results that emerged during the policy forum.

Return of results in clinical settings

The central controversy surrounding return of results from whole genome or exome sequencing tests in clinical settings is whether patients should have the choice of receiving secondary findings that are detected during testing that was performed for other purposes. The panelists expressed opposing viewpoints on this controversy. Lainie Ross, MD, PhD, Professor of Clinical Medical Ethics at the University of Chicago, pointed out that patients have the right *not* to be informed of results from genetic tests for reasons including: the information may not be relevant for decades, the information may inaccurately predict risk, the information may only be wanted if effective treatments or preventions are available, and the tests may reveal unanticipated information that might produce harm (e.g., misattributed paternity). Other experts believe that the rationale for treating return of results of secondary/incidental findings from genomic sequencing differently than return of results from other types of medical tests is unclear [5]. Laura Bierut, MD, Professor of Psychiatry at the Washington University School of Medicine raised this issue during her opening remarks in a thought experiment. If a patient gets a chest X-ray and the radiologist notes a lesion incidental to the purpose of the imaging, shouldn't the radiologist tell the doctor and the doctor tell the patient? She emphasized that if the healthcare provider believes that the finding may be life changing, that it should be provided to the patient. For further discussion of this analogy see Solomon 2014 [9]. Ellen Wright Clayton, JD, MD, Professor of Pediatrics at Vanderbilt University School of Medicine and Professor of Law at Vanderbilt University School of Law, emphasized the point about definitions of types of findings in her opening remarks; the ACMG recommendation for reporting variants in 56 genes does not actually constitute reporting of 'incidental' findings as was defined by the ACMG report. One must actively search for, sequence and analyze these genes for variants, which as Dr. Ross noted, mandates the addition of opportunistic screening any time whole genome sequencing is performed. It requires the clinical laboratory to actively sequence, analyze, and interpret variants in 56 highly penetrant genes, and if found, report them back to the physician. She believes that this poses serious ethical issues including: (1) it does not require the consent of the ordering physician or patient, and (2) there is predictive uncertainty—i.e., pathogenic variants in genes identified by the ACMG may be highly penetrant in high-risk populations where the most research has been conducted but it is unclear whether the same is true for populations where research has not been conducted.

Return of results in research settings

The issues surrounding return of results from genomic sequencing studies in research settings differs from clinical settings. Jonathan Green, MD, Executive Chair of the Washington University Institutional Review Board (IRB) reminded the audience that the IRB is charged with determining that research involving human subjects meets specific regulatory criteria (45 CFR 46.111) that are derived from the Belmont Principles [10]. Human subjects' regulations require that informed consent include a statement that the study involves *research*. Returning genetic information, particularly if unrelated to the aims of the study, crosses into the realm of clinical medicine. Individuals who enroll in research studies where there is a promise made to return results and secondary findings, are likely to equate this with going to their primary care doctor and having a test done for clinical purposes. Dr. Green noted that the informed consent document must include a description of any reasonable foreseeable risks or discomforts as well as benefits to the subject. Because anticipated and secondary findings that are generated in genomic research meet the standard of being reasonably foreseeable, the informed consent process must clearly disclose the possibility of returnable results and secondary findings and their implications for the participant. It is less clear, according to Dr. Green, whether returning results on secondary findings should be considered a risk or a benefit. In ideal circumstances, the benefit is obvious. That is to say, the participant is made aware of a medical condition for which an action can be taken, and a poor outcome is averted. However, Dr. Green stressed that potential harms may also occur when participants receive results including unnecessary additional tests and procedures each with their own associated costs, risks, and morbidities. For example, the penetrance of *BRCA1* pathogenic variants may be lower in the general community than in those women who have a family history of breast cancer [11]. Returning results to women for rare *BRCA1* variants with uncertain penetrance could lead to potential harms including leading some women to undergo prophylactic measures to reduce their risk [12,13].

Dr. Green discussed the current state of affairs for guidelines on return of results in research settings. Current United States regulations require that participants be fully informed about the nature of the research, and therefore they must be informed about the possibility of research results or secondary findings being generated in a study. Furthermore, they must be informed about what the researcher plans to do with the information (return them or not). If results are to be returned, participants should be asked at the outset whether they want the results, ideally at the time of informed consent, and then perhaps again at the time they are available. When returned, risks must be minimized by assuring the results are valid and that the participant is provided with appropriate resources and follow-up to act on the information. Dr. Green stated that he does not believe that current regulations require researchers to routinely look for secondary findings, nor to always promise to return research results or secondary findings. Nor does he believe that it should be made mandatory for researchers to do so. Mandating return of results promotes confusion between the roles of researcher and clinician, as well as the roles of participants and patients. Research is not clinical care and the researcher–participant relationship is not the same as the physician–patient relationship. Researchers should be wary of accepting new obligations that cross over into the clinical realm. Imposing a mandatory duty on all researchers to look and warn,