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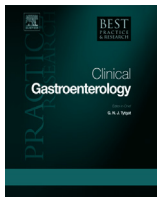

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Ethical issues raised by whole genome sequencing

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A B S T R A C T

While there is ongoing discussion about the details of implementation of whole genome sequencing (WGS) and whole exome sequencing (WES), there appears to be a consensus amongst geneticists that the widespread use of these approaches is not only inevitable, but will also be beneficial [1]. However, at the present time, we are unable to anticipate the full range of uses, consequences and impact of implementing WGS and WES. Nevertheless, the already known ethical issues, both in research and in clinical practice are diverse and complex and should be addressed properly presently. Herein, we discuss the ethical aspects of WGS and WES by particularly focussing on three overlapping themes: (1) informed consent, (2) data handling, and (3) the return of results.

Introduction

In the last decade, the development of high-throughput and massively parallel DNA sequencing technologies, also known as next generation sequencing (NGS) technologies, has resulted in a substantial reduction in the cost and time needed to sequence an entire human genome. The Human

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Genome Project lasted over a decade, cost three billion USD and resulted in the sequencing of basically one human genome. Meanwhile, in January 2014 the company Illumina announced that it could sequence a human genome for the fabled price of 1000 USD (an albeit relatively arbitrary and likely more psychological price threshold) in less than a day [2]. Although Illumina's price tag is undoubtedly on the low side of the present range of prices, it is still in line with the costs presented by The National Human Genome Research Institute's yearly update on WGS costs, which was estimated at between 5000 and 10 000 USD in 2013 [3]. As highlighted by Dr. Euan Ashley, director of the Clinical Genome Service and the Center for Inherited Cardiovascular Disease at Stanford University (USA), this reduction in price would be similar to an expensive car with a price tag of 400 000 USD at the time of the Human Genome Project falling in price such that it cost only 40 cents today [4]. Such a dramatic drop in price obviously increases the accessibility of NGS so that whole genome sequencing (WGS) or whole exome sequencing (WES) are now within the reach of an exponentially growing number of researchers and physicians and by extension, patients and research subjects as well.

What is NGS and what can it do?

'"Next-generation" and "massive-parallel" DNA sequencing are blanket terms used to refer collectively to the high-throughput DNA sequencing technologies available which are capable of sequencing large numbers of different DNA sequences in a single reaction (i.e., in parallel).' [5] NGS tools allow for the sequencing of entire genomes, but they can also be used to sequence only targeted regions of the genome. For example, one can sequence only the protein coding regions of the genome (the exome), which is referred to as whole exome sequencing (WES),[1] or one can sequence only certain gene families (e.g.: globin genes) or genes involved in a particular biological pathway or associated with a particular (set of) disorder(s) (e.g.: colon cancer). Hence the tools provide many new opportunities to sequence more DNA faster and cheaper, but they also allow us to perform more or less the same experiments or testing we performed previously but more efficiently. Furthermore, it is also important to note that NGS enables the study of more than just the DNA sequence and its variations: it also allows for the study of RNA sequences and hence the study of the transcriptome (the genes transcribed from DNA, which also includes untranslated regions) as well as the study of epigenetic phenomena including DNA methylation and chromatin analysis. Casey and coauthors [6] review these applications in the specific context of gastrointestinal (GI) malignancies including the identification of germ line DNA markers for disease risk assessment and diagnosis; the identification of germ line or somatic DNA changes in order to help classify GI malignancies and/or be an indicator of therapeutic response; and allowing for the sequencing and analysis of the gut microbiome, which could lead to novel drug targets. The applications for transcriptome and epigenetic studies also raise practical and ethical issues that are related to and overlap with germline DNA sequencing and the study of variations (which is, presently, the most popular subject of debate when it comes to discussing WGS) [7], however we will focus our discussion herein on issues related to the latter application, and specifically to whole genome and whole exome sequencing.

In the clinic, WGS has enabled a new approach to how to diagnose patients with an unclear clinical diagnosis and allow for the study of many more genes than a relatively small subset of genes traditionally associated with the patient's condition [8]. Furthermore, even if a targeted approach is adopted, the use of NGS may reduce the time and hassle of the 'diagnostic odyssey' by sequencing all genes known to be involved in a disorder at once instead of sequentially [6]. Hitherto, WGS has been most useful in the clinic, by aiding to diagnose diseases 'that present with atypical manifestations, are difficult to confirm using clinical or laboratory criteria alone, or otherwise require extensive or costly evaluation' and for which not all genetic variants are known [9]. These conditions tend to be genetically heterogeneous, and often have large variation in their phenotypic expression such as intellectual disability, congenital malformations and mitochondrial dysfunctions [9].

[1] For the purposes of this article, the abbreviation 'WGS' will also be used to include whole exome sequencing, unless otherwise specified.