

## Challenges in the clinical application of whole-genome sequencing



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As the cost of sequencing the human genome falls, medical use of whole-genome sequencing will rapidly advance.<sup>1</sup> In this Viewpoint, we consider the opportunities and challenges that medicine will face in coping with the foreseeable flood of genomic information. Clinical genetic testing in adults is at present typically done for a few patients who, as a result of family history or clinical indications, are considered at risk of carrying genetic variations that are linked to a particular disease or disease predisposition. Additionally, some companies offer genome-wide genotyping of single nucleotide polymorphisms, providing limited information about disease risks and often bypassing the medical system to go directly to consumers. Reduced sequencing costs seem likely to cause a rise in whole-genome sequencing.

Compared with present clinical genetic testing, whole-genome sequencing greatly expands the breadth of testing from genes associated with a particular disease to the whole genome and, potentially, all the information that the genome contains about diseases or traits. By comparison with testing for single nucleotide polymorphisms, whole-genome sequencing crucially increases the possible strength of information about associations with diseases or traits. This prospect presents great opportunities and challenges for clinical medicine.

Informed consent requires that a competent patient be provided with sufficient information about a procedure and the associated benefits, risks, and limitations to make an informed decision about whether to proceed with treatment. The benefit of any genetic testing is increased knowledge about disease risks and predispositions, and, more tailored drug therapy (pharmacogenomics). Patients' interests in acquiring this knowledge, and their responses to it, vary greatly. Increased knowledge can result in medical or lifestyle changes that reduce risks, or it can affect the patient's life decisions or strategies for coping. Risks of genetic testing also centre on the accuracy of the knowledge that patients (or others) take away from the tests and how that knowledge is used. The vast amount of knowledge that is offered by whole-genome sequencing makes informed consent for this procedure more complex than that for existing genetic testing.

Patients need to be warned that most sequence information obtained will be of unknown meaning and importance. Present clinical genetic tests can often provide a patient with meaningful information about risk for one particular disorder, whereas very little of the whole-genome sequence data will have any associated meaning. Patients should be warned that they might learn that they are at substantially increased risk for one

or more serious diseases. For example, a patient could learn that he or she has a genetic predisposition for sudden cardiac death. Such risks could be suspected because of family history, or might come as an unpleasant surprise.

Patients should be told that as part of the interpretation of whole-genome sequencing, analysis of single nucleotide polymorphisms will show that they have slightly altered genetic risks for common adult diseases such as cardiovascular disease, diabetes, and various cancers. These disorders will have both genetic and environmental components; some might have useful interventions, but others will not. They should be cautioned that for many of these risks, what actions, if any, they should take will be unclear. Furthermore, patients should be warned that whole-genome sequencing might reveal information about risks for sensitive issues, such as psychiatric disorders or behavioural traits. At present, clinical genetic testing examines only a few risks, which are specified in advance. Whole-genome sequencing will potentially provide information about countless medical conditions.

In view of the predicted frequency of recessive mutations in the population, every patient will learn that he or she is a heterozygous carrier of more than one serious or lethal autosomal recessive disease. This information might affect a patient's reproductive decisions, and have implications for existing children or other relatives. Since whole-genome sequencing will show that every patient has an above-average risk for some disorders, and for having children with some genetic diseases, every patient could face some negative social consequences from those risks, whether in insurance, employment, stigma, or otherwise. Although, in the long run, recognition of the universality of risk might lead to improved social support, in the short term, the patient might suffer.

Patients will put different weights on these risks as a function of their own circumstances and their own views about what is important in their lives. Thorough discussion of all risks before patients decide whether to be tested will allow people to make a decision that is right for them. Additionally, patients often have poor knowledge of genetics and have difficulty understanding and applying ideas of risk and probability.<sup>2</sup> To make informed decisions about whole-genome sequencing, patients will need to have the opportunity to ask questions of, and get accurate answers from, knowledgeable and trained professionals. This process will be difficult, lengthy, and expensive, but how the consent process could be meaningfully undertaken in any less intensive way is hard to imagine.

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**Panel: Practical considerations for use of whole-genome sequencing data in clinical practice**

- The broad scope of the results will require that patients receive complex and detailed information before they decide whether to be tested
- Interpretation of genome sequences should take into account the limits of the sequencing method used
- Easily accessible and well curated information about the links between genomic sequences and diseases needs to be created, maintained, and frequently updated
- Physicians and patients will have to cope with enormous uncertainty in some results, particularly around variants of unknown importance, which might require analysis of genetic information from family members
- Effective ways to convey meaningful information to patients about the many implications of their whole-genome sequences need to be developed and training for appropriate specialists to convey this information funded
- Whole-genome sequences will need to be reviewed regularly to incorporate new information about disease risks, and changes in assessment will have to be conveyed to patients

The process for clinical annotation of a patient's whole-genome sequence is new and complex. Little of the interpretation will be easy; much will be very difficult, for at least three reasons. First, specific sequencing methods will have limitations that need to be understood. For example, some methods do not reveal translocations, large duplications or deletions, copy number repeats, or expanding triplet repeats. When two variations are identified in the same gene, present whole-genome sequence analyses cannot be used to establish whether those variations are in copies of the gene on different chromosomes or in the same copy of the gene—a distinction that is crucial for recessive disorders.

Second, interpretation of a whole-genome sequence requires good information about every known genetic disease and pharmacological risk. That information is difficult to obtain, and is very hard to keep up to date. No centrally maintained repository of all rare and disease-associated variants currently exists. For a recent report on whole genome sequencing,<sup>1</sup> we spent hundreds of hours reviewing independently-curated disease-specific databases, analysing the annotated pharmacogenomic database, Pharmacogenomics Knowledge Base, searching PubMed and Online Mendelian Inheritance in Man, and implementing predictive algorithms to assess variants. Interpretation of the patient's genome involved the work of a clinical geneticist, a genetic counsellor, and experts in bioinformatics, genetic cardiology, internal medicine, and pharmacogenomics, among others. Efficient risk analysis of whole-genome sequence

information will need improvement of methods, with substantial automation.

Third, whole-genome sequencing will reveal many unusual or previously unknown genomic variants of uncertain importance, either in general or for a particular patient. Both raise challenges. For example, many variants identified through whole-genome sequencing will be benign, but sequencing might result in a large increase in testing by cautious physicians to rule out false-positive results.<sup>3</sup> Such an increase would not only raise health costs, but would subject patients to the physical and psychological costs of increased testing. By contrast some previously unknown variations will terminate open reading frames, and thus be clear reasons for concern. Others will substitute one amino acid for another. What the patient needs to be told about these variants is unclear.

Even if a patient's whole-genome sequence is properly interpreted, the resulting information needs to be successfully conveyed to the patient. How will we do that? North America has about 2500 trained genetic counsellors and 1100 clinical geneticists. They are busy, providing information to patients about disease-directed genetic testing and the associated results. Although there is no doubt room for automated assistance in the interpretation, a knowledgeable human being will need to sit down with patients to explain, patiently and sensitively, the meanings of their genomes. Who will provide skilled interpretation of whole-genome sequence to millions of patients? Increased genomic knowledge for all physicians, improved referral methods, and approaches using electronic records and computer algorithms will all be needed.

The rapid growth of genetic knowledge also raises difficulties. A genome is interpreted in view of present knowledge. Tomorrow that knowledge will be different. Some potential risks will have disappeared and new risks will have been reported. The magnitude of the risks will change as will our knowledge of the interaction of particular genomic risks with other genomic variations and with the environment. How will the patient's genome be reassessed in view of changing information, and how and when will new information be conveyed to the patient?

Even if individual professionals or groups of professionals with the relevant knowledge were available, they would need to be paid. We predict that an average person might need information about roughly 100 genetic risks discovered in their genome. Even if that information averaged only 3 min per disorder, this process would take more than 5 h of direct patient contact, after many hours of background research into the importance of the various genomic findings. Although evolving analysis and visualisation methods will undoubtedly help, how we can provide that much information in a meaningful way—and who will pay for it—is unclear.

Whole-genome sequencing is already occurring. Before very long all patients might have their genomes

For Online Mendelian Inheritance in Man see <http://www.ncbi.nlm.nih.gov/omim>

sequenced for medical use. We are optimistic about the value of whole-genome sequencing in medical practice, but implementation of such testing will be challenging (panel). As academics, we often assume that information is good and more information is better. But more information can sometimes be counter-productive. We need to begin thinking about when and how to offer full genome sequencing for clinical use. This preparation is essential to achieve maximum benefits from this technology, while keeping the harms to a minimum.

#### Contributors

EAA and HTG conceived of the idea for the report. EAA, MTW, AJB, and RBA prepared data for discussion. KEO and HTG prepared the draft. All authors contributed to revision and approved the final report for submission.

#### Conflicts of interest

RBA is consultant to a direct-to-consumer genetic testing company, 23andme, and has received consultancy fees from Novartis. KEO was a paid consultant as a member of the Genetic Counseling Task Force for Navigenics from June, 2007, to August, 2009. AJB is a scientific advisory board member and founder for NuMedii and Genstruct, is a scientific advisory board member for Johnson and Johnson, has received consultancy fees from Lilly, NuMedii, Johnson and Johnson, Genstruct, Tercica, and Prevedia and honoraria from Lilly and Siemens, and holds stock in NuMedii and Genstruct. EAA, HTG, LH, TEK, and MTW declare that they have no conflicts of interest.

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