



Challenges to Whole Genome Sequencing in National Healthcare Systems

Steven Witte, Wellcome Trust Sanger Institute, University of Cambridge

Whole genome sequencing (WGS) technology, which is used to decipher the entire genetic code of an individual, has recently passed a major milestone. Last year, the sequencing technology company Illumina announced that they can now sequence an individual's genome for \$1,000. This price has long been thought of as the one which could make it feasible to undertake the widespread adoption of WGS as a service of national health systems [5]. Media coverage of this technology is frequently sensational and focuses on potential dangers such as intrusion upon people's private information by the government or insurance companies or on eugenics and genetic determinism. Thus, the media often overshadow more meaningful discussion of how WGS may influence our future. It is time for policy makers to anticipate the adoption of WGS, and consider its potential harms and benefits.

What exactly does WGS promise? Personalized, or individualized, healthcare. Current medical practice depends on average results from clinical trials to determine the optimal treatment for diseases. However, with the advent of personalized healthcare, patients are beginning to receive drugs that are predicted to be most effective or give the least side effects based on their genetics. Additionally, WGS could be of benefit for preventive medicine by revealing diseases patients are genetically predisposed to, allowing doctors to recommend appropriate lifestyle changes for patients. An especially controversial potential use of WGS is as part of

routine screening of newborns or fetuses. Based on WGS information, parents, or those soon to become parents, could make decisions about the future of their child or foetus, for example regarding plans for the child's lifestyle or whether to terminate a pregnancy.

The challenge for policy makers is to put a framework in place that allows these promises to be delivered in ways that maximize their benefits and minimize harms. Unfortunately, there is little helpful information available to the public to give an unbiased portrayal of the issues WGS poses for us. However, in parallel with sensational stories in the media, an unofficial yet fruitful conversation between biomedical scientists, doctors, and social scientists has been growing quickly.

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Below, I have summarized central issues covered in these discussions, including challenges of interpreting genomic data, lack of genomic education in healthcare systems, ethical issues surrounding incidental findings, newborn or infant screening, and privacy/data storage issues. Available research consensus and policy positions from notable organizations are included as well.

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Practical Issues

Current effort involved in genome sequence analysis

Sequencing technology has matured rapidly; analysis of the resulting data is now the bottleneck that needs to be resolved. Currently, sequencing data can only be analysed by experts with the help of complex computational tools. If WGS is to become a common medical test, the analysis methods for the test results need to develop apace. These methods need to become faster and easier to use so that analysis can take place at the required scale. Additionally, although an individual's genome can be sequenced for \$1,000, this price does not take into account the specialized analysis required. While the cost of analysis is difficult to estimate, at the moment it may well increase the total price several-fold.

Lack of education of health care professionals

Many patients, and even clinicians, view genetics as highly deterministic, when in reality this is not usually the case. Often, a mutation will increase the likelihood of a disease manifesting itself in a person by only a small amount. Genomic medicine is currently not typically included in medical, nursing, or other healthcare curricula, and even if it were added now, the challenge of educating existing healthcare workers remains. To improve education, questions on genomic medicine could be included on board and licensing exams. Also concerning is the inadequate number of genetic counsellors. For WGS to successfully become a widespread test, professionals are needed that can counsel patients on their results. Employing these counsellors would also further increase the total price of WGS.

Cost and security of data storage

The process of sequencing an individual's genome produces a large amount of computational data that requires tens of gigabytes of memory. The data of just a small number of genomes would overwhelm a laptop or desktop computer, which is why expensive servers are needed to handle central storage. If WGS were performed for a significant percentage of the population, the storage costs would be

substantial. This in turn would drive up the price of WGS as a medical test. Privacy is also an issue. Concern has been raised about companies gaining insight into an individual's genetic makeup to help decide whether they will hire them, and about insurance companies accessing WGS data to make decisions about coverage for an individual. Therefore great care must be taken to ensure patient data is stored securely.

Ethical Issues

Interpretation and incidental findings

Scientists have spent decades compiling databases of genetic mutations that are associated with diseases, which are becoming more comprehensive every year. But some of this research is of insufficient quality, mostly in earlier studies performed when research methodologies were less reliable. Scientists estimate that 25% of reports linking a gene to a disease are incorrect (Bell, 2011). It is essential that the only mutations flagged as harmful in WGS tests are those supported by broad scientific consensus to have a role in disease. Otherwise, patients could falsely be told they may develop a serious disease, potentially causing them psychological harm and making healthcare professionals targets of malpractice lawsuits.

When a patient has their genome sequenced, it is possible that an unexpected disease-associated mutation may be found. For example, the sequencing of a cancer patient's genome to determine the optimal drug for them may also uncover that they are likely to have Alzheimer's disease when they are older.

In other medical tests, incidental findings are usually shared with the patient – if a radiologist sees a tumour underneath a cloud of pneumonia on an x-ray film, the patient will be alerted and provided appropriate care. But in most tests, these incidental findings are relatively rare. WGS is different: the genome contains 20,000 genes, thousands of which can contain disease-associated mutations (Hamosh, 2005). The chance of seeing something unexpected is much higher in each patient.

The best way to handle these incidental findings is under debate in scientific and medical communities, since clinicians will need clear ethical guidelines for their practice. The debate is about protecting the patient, whilst also respecting their ability to control their health and have all the information they want, which medical ethicists refer to as patient autonomy. Often it is suggested to only return incidental findings that can be addressed, that is findings regarding diseases that can be prevented or cured.

Some research has been conducted investigating how much information people would like to learn about their genome. Middleton *et al.* interviewed hundreds of individuals to find out their thoughts when hearing their incidental findings from a WGS test. Most wanted the information, especially if it concerned diseases for which cures or preventive treatments exist. However, it has also been shown that individuals do not modify their behaviour when they become aware of genetic risks they face (Hollands, 2016). More large-scale studies need to be done to confirm these findings, as has been done for incidental findings from imaging tests.

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Professional organizations have set out recommendations for clinicians and policymakers. For the full explanations I recommend the original documents, but I have summarized some of the main points:

American College of Medical Genetics (ACMG)

- Supports patient autonomy
- Recommends adequate pre-test counselling and informed consent to see if the patient would like to receive incidental findings
- Recommends that only mutations known with certainty are returned – those with tests that can confirm them, are preventable, and have treatments

- Incidental findings should be returned regardless of age

Association of Genetic Nurses and Counsellors (AGNC)

- Supports patient autonomy
- Incidental findings for adult-onset diseases should not be returned to children
- Recommends that a pre-determined list of mutations be made. This list should be well-validated scientifically, and mutations should only be involved in diseases that are serious or life-threatening and for which there are interventions or preventative strategies available

Genome screening of fetuses or newborns

There is dispute over whether to give children knowledge of a disease they will or are likely to develop as adults. This needs to be resolved, as many propose using WGS on all newborns as part of newborn screening.

In the UK, newborns are screened for conditions such as congenital heart defects, cystic fibrosis, and sickle cell disease. Screening programs are highly scrutinized by regulatory agencies to ensure quality and cost-effectiveness.

A practical problem with screening all newborns by WGS is the total cost for the healthcare system. The big question is whether any incidental findings made about each newborn would need to be followed up by doctors to validate them and prescribe treatments accordingly. The costs of doing so are difficult to estimate, but are likely prohibitive (Beckmann, 2015).

A contentious issue is involved in testing fetuses. In response to WGS screening results, expecting parents could have the ability to terminate a pregnancy if the foetus does not have the genetic traits they want. Although this is a choice many expecting parents already must make for conditions such as Downs Syndrome (for which a blood test exists that is elective in the UK), it

remains an area of controversy. Once we know more about how genetics influences complex traits like intelligence or athletic ability, WGS information will not only be informative about the future health of the foetus, it may in theory also be used to predict how smart or good at sports a child could become.

The AGNC recommends that opportunistic genomic screening should be available to all children and adults. However, others have cautioned that little research has been conducted to understand how parents and children may react to undesirable results. Until more is known about the benefits and harms of using WGS as a screening tool, it may be best to use it only when needed to diagnose a disease.

Recommendations

- I. Policy makers should recognize the potential benefits of genome sequencing for public health but also take into account and address ethical and practical issues.
- II. Legislation should be considered concerning issues of adoption of WGS into the NHS, return of results to patients, and data storage. Specifically, funding for WGS tests, guidelines for providing WGS tests and their results to patients, privacy issues, and protection from genetic discrimination need to be addressed. See Knoppers *et al.* (2015) for a comprehensive list of policy recommendations made by professional organizations and legislation passed in several countries.
- III. Funding should be continued for quality research to find cures or preventive measures for various genetic diseases as well as to uncover new disease-associated genetic traits. Furthermore, funds should be allocated for studies that will re-examine genes reportedly linked to diseases, so that false links can be eliminated. In addition to these genetics studies, social science investigations into the psychosocial effects

and ethics of WGS testing are important and should receive funding as well.

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About the Author



Steven Witte is an MD/PhD candidate and an NIH Cambridge Scholar. He performs research on immune disorders using genomic approaches. As a freelance writer, Steven writes about science policy, patient advocacy, and genomics.

Steven is also a member of the Board of Directors for Universities Allied for Essential Medicines.