phg foundation
making science work for health

Whole genome sequencing

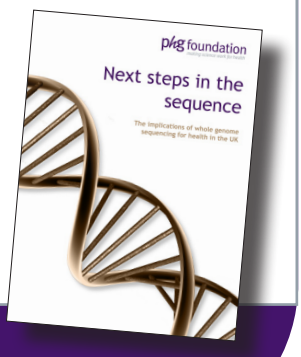
Clinical impact and implications for health services

Recent rapid developments in DNA sequencing technologies have dramatically cut both the cost and the time required to sequence a human genome, such that it may sooner be easier and cheaper to sequence an entire genome than to extract and test relevant sections for a number of known mutations. Combined with our advancing understanding of genes and disease, whole genome sequencing is set to change current clinical and public health practice by enabling more accurate, sophisticated and cost-effective genetic testing.

In the light of these changes and building on our own expertise in this area, the PHG Foundation undertook a ground-breaking project to evaluate the implications of these genome sequencing technologies for health services, with a focus on the UK National Health Service (NHS). We brought together leading experts and stakeholders to address the following issues:

- What is the role of new DNA sequencing technologies in medicine and population health, in the short to medium term, and how will they alter or augment routine practice?
- What ethical, legal, social and economic issues are raised by whole genome sequencing?
- What are the implications of whole genome sequencing for diagnostic services within the UK and health services more generally?
- What operational barriers exist to adoption within health services and how should they be tackled?

The new report, *Next steps in the sequence*, provides the first comprehensive overview of the short to medium term medical impact of human genome sequencing, identifies key issues and barriers to use in the NHS, and provides informed recommendations for optimal implementation of these wide-ranging and potentially disruptive technologies.



UK scenarios and expert recommendations

Using WGS for health

Whole genome sequencing (WGS) differs from traditional genetic testing because of the sheer volume and complexity of data it generates; each genome contains 3-4 million genetic variants that differ from the reference human genome sequence, most with no definite medical or personal significance. Cancer cell genomes have numerous additional genetic changes superimposed on the patient's inherited genome, but only a few will be clinically significant. Understanding the health impact of individual genomic variants presents a considerable challenge for analysis, interpretation and management of data.

Assay - sequencing a genome

Provides no medical information per se; *cost and time have fallen dramatically*

Test - analysing genomic sequences for a specific purpose

Interpretation directed by expert knowledge of genomic variants, disease risk and clinical features; key bottleneck for application of WGS in medicine

Although new knowledge emerges almost daily, the medical impact of most genomic variants remains unknown, making interpretation of test results extremely difficult. However, the process can be greatly simplified by targeting only selected variants relevant to the clinical question for analysis. In practice, this will necessitate new bioinformatics tools and a robust evidence base.

Applications in inherited diseases

Analysis of WGS data for diagnosis of inherited disease should address a specific clinical question, to maximise effectiveness and avoid overwhelming clinicians and patients with irrelevant or uninterpretable information. Where a specific diagnosis is suspected, only known disease-associated genetic variants with good supporting evidence should be selected for testing; this is essentially a closed-ended test and can be evaluated in the same way as any other diagnostic. This type of testing will increasingly be used in different mainstream medical specialties. Where the possible diagnosis is unknown, genome-wide investigation will be required, but the test should aim to identify only novel or rare variants; this is an open-ended form of test, making evaluation harder due to the absence of a single gold-standard test for comparison. This sort of testing may remain within the realm of clinical genetics.

Applications in oncology

WGS offers a unique opportunity to better understand the genetics of cancer and improve diagnosis, management and prognosis for individuals with the disease, especially common, solid tumours such as breast, lung and colorectal cancer. Genomic analysis will need to identify clinically important variants in an individual's cancer genome. Once a comprehensive catalogue of cancer-causing mutations has been compiled, along with good evidence for the clinical validity and utility of cancer genome testing, this application could offer substantial health benefits for the majority of the population at some point in their lives.

Recommendations for the use of WGS within the NHS

(1) NHS use of genome sequencing

Advanced sequencing technology should be implemented in the NHS in the short to medium term where it offers clear clinical or cost benefits over existing tests, for example the diagnosis of inherited diseases and the management of cancer.

(2) Clinically targeted analysis

Analysis of genomic data (and reporting to patients) should be confined to variants relevant to the medical condition of interest; wider analysis for preventive purposes is not recommended without a compelling clinical reason.

(3) Biomedical informatics

The NHS should urgently develop clinical bioinformatics expertise and infrastructure, to ensure technical support for medical analysis and interpretation of genomic data. The best way to do this may be by establishing a National Biomedical Informatics Institute and new posts for bioinformaticians in local clinical services.

(4) Developing the evidence base

The new National Biomedical Informatics Institute should create and maintain standardised databases of normal and pathogenic genomic variation with linked analytical tools to facilitate clinical use.

(5) Policy development

Policy research is needed to define the evolving relationship between the health service and patient, their respective rights and responsibilities in the context of genomic analysis, and to develop professional guidance for clinical use of WGS.

(6) Competences and best practice guidelines

Competences and best practice guidelines for genomic analysis should be developed for health care professionals.

(7) Service provision

A modular approach should be taken, with a small number of sequencing laboratories (or providers) acting as regional hubs to provide national coverage to the NHS.

(8) Health economics

Outcomes evidence and health economic modelling of the impact of genomic analyses are urgently needed to identify costs and savings.

(9) Commissioning

Rational, clear and transparent commissioning pathways need to be developed by all relevant stakeholders, to ensure effective and fair clinical delivery of WGS.

(10) Genomic screening

Policy research is needed to consider under under what conditions opportunistic screening of the genome might be offered, and what issues might arise.

Next steps in the sequence

Wider issues

The expert group concluded that the NHS has no duty of care to screen an individual's genome or offer tests except for specific, evidence-based medical purposes. If people choose to have their genome privately sequenced and analysed, the NHS should provide follow-up advice and care only for findings of significant clinical relevance in that individual.

WGS has the potential to increase incidental findings, since an individual's genome may contain multiple variants of medical significance. Using targeted analytical strategies focusing on specific clinical questions in genomic analysis will minimise (though not eliminate) such findings, and health care professionals should only be obliged to tell patients about those that are unavoidably discovered and medically important. In the long-term, it may become appropriate to use genome analysis more opportunistically for screening, looking for genetic variants associated with treatable or preventable outcomes to improve individual and population health.

Conclusions

The application of WGS has major implications for both human and IT resources within the NHS. It is dependent on robust and extensive databases of population genome variation and genotype-phenotype correlations, in addition to standardised, purpose-built algorithms for selecting variants of likely relevance to the clinical question. It is not dependent on storing genome sequences, but will rely on storing aggregated anonymised data to aid and improve interpretation of novel variants. Crucially, health care professionals, patients and the public must be clear about the purpose and limitations of whole genome analysis services offered by the NHS.

About us

The PHG Foundation is an independent genomics think-tank based in Cambridge, UK. We work closely with academia, the healthcare and corporate sectors. As a charitable foundation, we use our multidisciplinary expertise to identify and evaluate biomedical innovations with the potential to improve health globally, and to encourage adoption by health systems.

To find out more

The full report, *Next steps in the sequence*, is available from our website, along with other reports and the free *Genomics and Policy News* service.

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