

Genomic Medicine

Submission to House of Lords Science and Technology Select Committee Oxford Nanopore Technologies Ltd April 2008

Introduction

Oxford Nanopore Technologies Ltd ('Oxford Nanopore') welcomes the House of Lords Science and Technology Select Committee's inquiry into genomic medicine and is grateful for the opportunity to contribute evidence on this important subject.

The successful introduction of genomic medicines relies on a complete process from basic research, through drug discovery and development and integration of medicines or techniques into practice. DNA sequencing technology is a key and rate-limiting part of this process, and the technology under development at Oxford Nanopore has the potential to accelerate the growth of genomic research and development.

Executive Summary

Oxford Nanopore is a British company, spun out of the University of Oxford in 2005 and founded on the science of Professor Hagan Bayley. It is developing new technology that has the potential to improve greatly the speed and cost of DNA sequencing. Currently, DNA sequencing is expensive and slow, and this is a limiting factor in the development of genomic medicine. Oxford Nanopore's technology is being developed to allow DNA analysis to be performed without amplification or labelling, the two steps that limit current methods. These qualities allow for dramatically faster and cheaper DNA analysis. A technology with these qualities will therefore enable a major acceleration in the progression of genomic knowledge and the development of genomic medicine.

Nanopore technology is poised to impact genomics research in academia and industry worldwide, with major implications for healthcare. However, the lack of clear funding mechanisms that are specific to emerging genomic technologies risks undermining future advances and their potential benefits for the NHS and UK economy.

It is accepted that the area of genomic medicine raises many ethical, clinical and regulatory questions, and that public confidence in genomics is fragile, as highlighted by recent concerns over genetic privacy and direct-to-consumer genetic testing. The Government should anticipate a rapid acceleration in developments in genomic medicine. Expert debate, public engagement and the creation of a robust regulatory framework is urgently needed to safeguard the future benefits of these medical advances.

What is the state of the science and what is the rate of change?

Basic research: *“The current challenge is to reach a price-performance point [in DNA analysis] that would enable previously impossible genome-wide studies. Making use of genomic information will require extensive validation of correlations between mutations and phenotype. This can be done either by large-scale association studies, bioinformatic predictions, or biological methods. Only then can genetic information be used to explain many facets of human life and society.” Genetic Engineering News, 2007*

Drug/diagnostic development: *“Pharmaceutical companies will be able to discover potential therapies more easily using genome targets. Previously failed drug candidates may be revived as they are matched with the niche population they serve. The drug approval process should be facilitated as trials are targeted for specific genetic population groups --providing greater degrees of success. The cost and risk of clinical trials will be reduced by targeting only those persons capable of responding to a drug.” Human Genome Project on pharmacogenomics¹*

The development of genomic medicines is driven by understanding of the relationship between genotype (the genetic code of an individual) and phenotype (the physical manifestation of that code, this may be a disease, condition or a risk factor, or an individual's specific response to a medicine). Although the volume of available genomic data is significantly larger than even two years ago, it is acknowledged that there is still an enormous amount to achieve. We describe here two areas in which knowledge is developing:

a) Basic research: Understanding of the influence of genotype on disease

There is currently a considerable research focus on specific genetic variations called Single Nucleotide Polymorphisms (SNPs). A SNP is seen when a single nucleotide, or 'DNA base' in one human differs from the standard sequence in a human genome. This genetic variation can result in errors in protein production and therefore influence disease.

“New technologies that are slashing the costs of sequencing and genome analyses will make possible the simultaneous genome-wide search for ... SNPs and other DNA alterations in individuals. Already, the unexpected variation within one individual's published genome has revealed that we have yet to fully comprehend the degree to which our DNA differs from one person to the next. Such structural and genetic variety is truly the spice of our individuality.”

Science, 2007: “Breakthrough of the Year: Human Genetic Variation”

The International HapMap project has progressed the catalogue of known human SNPs; In 2007, phase 2 of the project was reported, and the map now includes 3 million SNPs, representing between 25-33% of all human SNPs with frequencies above 5%. Genome-wide association studies generate understanding of the genotype-phenotype relationship by revealing which SNPs are associated with which diseases or conditions. To date approximately 130 such studies have been published, and reveal genetic variations associated with diseases such as prostate cancer, systemic lupus erythematosus, obesity and schizophrenia. However, examining only SNPs has serious limitations, as the full complexity of the genetic influence on disease cannot be seen, and only common diseases can be examined.

Ultimately, researchers aim to compare the complete sequenced genomes of many patients with a disease against a control group, rather than their lower-resolution 'scanned' genomes. At a cost of several hundred thousand dollars per complete genome, this is not currently feasible. However, with a potential step-change in sequencing cost and power on the horizon, this may be possible within years. Several major genome projects have been initiated, in the understanding that technologies will evolve. For example the 1000 genomes project aims to sequence 1000 individuals to gain a much higher-resolution map of genetic variation that will support future disease studies. The UK's Wellcome Trust Sanger Centre will play a major role in this project.

b) Drug/diagnostic development. Understanding of the relationship between genotype and drug response

Accessible genome sequencing will allow pharmaceutical companies to correlate drug efficacy and adverse events with patients' genetic profiles. This vision of personalised medicine only becomes achievable when genome sequencing is fast and cheap enough to be routinely integrated into the drug development process.

In summary, it is believed that a new technology that makes powerful genome sequencing available at a reasonable cost will accelerate the understanding of the genetic cause of disease. This in turn will accelerate the process of discovering and developing new genomic diagnostics and treatments. Also, the ability to integrate genome sequencing into the drug development process will allow the development of more targeted treatments, bringing improved health outcomes and more cost-efficient treatment paradigms. Nanopore technology has the potential to deliver this step change in the speed and cost of genome sequencing.

What is the current research priority?

Genome sequencing: cost and speed

A large proportion of current genetic research focuses on the analysis of smaller, specific regions of the genome. However, researchers aspire to be able to sequence and analyse the complete genomes of large groups of humans. Genome sequencing performance is therefore frequently discussed in terms of the cost of a whole genome, despite the fact that this is not yet common practice.

An entire human genome has 3.2 billion base pairs, the same number of letters as 2,000 copies of *War and Peace*ⁱⁱ. At this time, early 2008, it is estimated that fewer than eight complete human genome sequences have been produced. The first, mapped by the Human Genome project, cost approximately \$3billion, the second \$100m and the third, that of the DNA pioneer James Watson, \$1.5millionⁱⁱⁱ. When considering the cost of sequencing, it is important to include the costs of instruments, reagents, labour and bioinformatics. It is estimated that the current cost of completing a human genome is in the range of several hundreds of thousands of dollars^{iv}.

In 2004, the US National Human Genome Research Institute (NHGRI), part of the National Institutes of Health (NIH), launched a \$38m grant programme to drive the cost of a human genome past the \$100,000 barrier to \$1,000. The only grant awarded outside North America was to Professor Hagan Bayley of the University of Oxford, for the development of nanopore technology towards DNA sequencing.

Limitations

Current sequencing technologies are limited by the following technical processes:

- The need to **amplify** (make multiple copies of) DNA before starting to analyse it. This process is time-consuming, complex and expensive. During the amplification process, errors may be integrated into the DNA copies
- The need to **label** the DNA. The four different DNA bases: Guanine, Adenine, Thymine and Cytosine (G, A, T and C) are so similar that existing methods use chemical labels to distinguish between the bases and record their sequence. This involves the use of expensive reagents, and a complex workflow that can use many skilled scientists and take many days.
- **Conversion of the signal**. By using fluorescent labels, the instruments measuring the DNA need to convert a photon signal into an electric signal, for digital analysis. Data storage, reassembly and analysis is resource-intensive; re-assembly of the data at the end of the process is one of the most complex stages, and may be likened to putting together a jigsaw that has many millions of pieces

It is these limitations that mean that routine genome sequencing is out of the reach of many researchers, a factor that limits the progression of genomic medicine. Only a technology that is

free of the steps mentioned above is expected to be able to deliver a step-change in the power and cost of genome sequencing, and enable the acceleration of genomic medicine.

Nanopore Technology

For nearly 20 years, groups of researchers in the US and UK have been exploring the potential to use nanopores to identify single molecules, and more recently to sequence DNA. This groundbreaking science has been celebrated on the front covers of *Nature* and *Scientific American*.

While the race towards a \$1,000 genome is being fought by a small number of companies, these technologies are largely based around new or improved labelling techniques. It is not only the scientific community that is interested in these developments. The financial community is following the space as an example of technology that will drive large-scale changes in healthcare. A recent analysis of the technologies by the investment bank UBS concluded that *“Nanopores are dramatically faster and cheaper than conventional [sequencing] ... nanopore technology could one day be the cheapest and fastest...approach”*

Nanopore technology is poised to deliver a new paradigm in genomic research. This would be a trigger for the acceleration in the development of new genomic diagnostics and treatments.

Does the existing regulatory and advisory framework provide for optimal development and translation of new technologies? Are there any regulatory gaps?

Consumer groups and others have repeatedly raised ethical concerns about the acquisition, storage and use of genetic information. The expected growth in genomic data and resulting genomic applications may increase these concerns and it is important that the Government considers fully the implications of imminent technological breakthroughs for privacy and discrimination issues.

There is already concern that companies selling direct-to-consumer genetics tests may mislead or exploit consumers. A significant reduction in the price of DNA sequencing is likely to increase the availability of such technology, necessitating sector regulation.

Oxford Nanopore believes that the complex and controversial issues that surround genomic medicine warrant extensive debate which must be facilitated by Government. This approach would reflect global best practice. For example, The U.S. Department of Energy (DOE) and the National Institutes of Health (NIH) devoted 3% to 5% of their annual Human Genome Project (HGP) budgets toward studying the ethical, legal, and social issues (ELSI) surrounding availability of genetic information. The UK's Human Genetics Commission is an excellent example of an organisation that can fulfil such a role, and Oxford Nanopore would welcome further government support of the HGC to expand the scope and volume of its work.

The technology under development by Oxford Nanopore would create a revolution in genetic research and a rapid acceleration in genomic healthcare. A robust, future-proofed regulatory framework that addresses both clinical and ethical issues should be developed in consultation with all stakeholders. This will ensure the stable introduction of new genomic medical treatments to the benefit of patients and the NHS.

How much cross-sector collaboration takes place?

Oxford Nanopore was founded so that the multidisciplinary skills required to create an amplification-free, label-free, nanopore DNA sequencing system could be assembled into one organisation. The company is closely aligned with the University of Oxford, and draws on an international network of world-class academics in the area of nanopores. This network includes

faculty members of Boston University, Harvard University and the University of California at Santa Cruz.

In the UK, Oxford Nanopore would welcome a greater emphasis on government support of cross-sector collaboration and suggests a review of its support of industry-academia collaborations. For example, Oxford Nanopore will be exploring research partnerships with UK scientific institutions, whether these are with existing genomics centres such as the Wellcome Trust Sanger Institute or other institutions that have an interest in genomic information.

How does the UK compare to other countries and what lessons can be learned?

The UK has traditionally led the world in the science of genetics. For example, Nobel prizes have been awarded to the team who determined the structure of DNA in 1953 and to Fred Sanger, who in 1975 developed a process to sequence DNA. Now, the UK Wellcome Trust Sanger Centre analyses more DNA than any other centre in the world.

The successful development of nanopore DNA sequencing technology would be regarded as an achievement on a similar scale. It would be used globally, by scientists and ultimately clinicians, to transform genomic medicine. In an area of science that is keenly followed, particularly in the US, the success of such technology would enhance the UK's reputation for excellence in innovation and science. We believe that the potential international impact and national benefits of genomic technologies necessitate greater cross-sector cooperation.

In other countries a strategic approach is taken that combines the development of genome analysis technology and the application of that technology in research. In the USA, for example, the National Institutes of Health (NIH) and Department of Energy (DoE) together fund more than \$1billion in DNA sequencing^v and the NIH is running a \$38m grant programme to support the development of specific technologies for DNA sequencing^{vi}.

We suggest that the Government review the support that it plans to offer academic institutions and emerging technology companies, towards an overall goal of taking a leadership position globally in the development of genomic medicine.

Oxford Nanopore is a domestic company with an international focus, which springs from one of the UK's most visible and reputable academic institutions, the University of Oxford. The company also has scientific and commercial relationships with some of the world's leading universities. We would welcome the opportunity to extend this partnership approach and to work more closely with Government to meet shared objectives.

What are the implications of developments in genomic technologies for the NHS?

Former Prime Minister, Tony Blair, said, as far back as 2003, that he was proud of the ground-breaking work already taking place in our country [in genomic medicine] and that he was determined that the NHS should be able to respond to these advances so that the benefits of genetics and more personalised medicine and improved healthcare should be available to all. In fact the NHS, as a universal provider of healthcare, is uniquely placed globally to maximise the potential benefit of personalised medicine.

Personalised medicine will aim to diagnose a disease early, or even before its appearance. Targeted drug therapies will aim to improve response rates and reduce adverse event rates. Overall the personalised medicine paradigm promises to reduce the aggregate cost of healthcare through better prevention, earlier intervention and improved management of disease.

Importantly however, such cost savings will be primarily population based and so most readily realised within a healthcare system that is not fragmented. In contrast to systems that do not offer universal coverage, such as that of the United States, the NHS could achieve maximum benefit

from this healthcare revolution and demonstrate to other territories how genomic medicines can offer both health outcome and economic benefits

Who is responsible for translation to clinical practice?

Oxford Nanopore would endorse the view of the Human Genetics Commission, as expressed in their submission to the Review of the Government Genetics White Paper; that the process for the development of genetics technologies from research laboratories to healthcare practice has been slow and ad hoc.

The UK's Wellcome Trust charity is at the forefront of influencing and funding research into genomics and promoting its translation into clinical practice, particularly at the Wellcome Trust Sanger Centre. The Trust is engaged in the support of new technologies for DNA analysis, basic research into the genome and its relationship with human health, and public education on genomics. Within government, progress has been announced in translational medicine but this does not yet have a rigorous, specific remit in genomics.

The Progress Review of the Genetics White Paper, published on 16 April 2008, notes that £70m has been invested in the area of genetics since 2001 to "*help the NHS make best use of the advances in genetics knowledge*". A framework has started to develop that will guide the introduction of genetics into the NHS, and in particular the formation of the National Genetics Education and Development Centre and the UK Genetic Testing Network are welcome. However, the pace of developments in the area of genomics is likely to accelerate in coming years and the government will face new challenges in clinical and ethical areas for which it needs to prepare.

It is essential that the investment in genetics is part of a long-term strategy to support innovation in the field and not a one-off event. This view appears to be upheld in the White Paper Progress Review: "*Genetics is still a relatively new area of work, and the review recognises that developments need to be considered over a longer timeframe, and will require sustained support.*" Oxford Nanopore would like to emphasise the importance of support for the whole process of developments in genomic medicine, from emerging technologies to improve DNA analysis through to the resulting clinical applications.

ⁱ http://www.ornl.gov/sci/techresources/Human_Genome/medicine/pharma.shtml

ⁱⁱ Gene Map: Help or Hype: www.wired.com 02.09.01

ⁱⁱⁱ <http://www.nature.com/news/2008/080416/full/452788b/table1.html>

^{iv} Recently, technology companies have made announcements that a genome had been sequenced for \$60k and \$200k, however these costs were only for reagents. A typical instrument cost for high throughput DNA sequencing is currently between \$500k and \$1,300k.

^v Kalorama: DNA sequencing equipment and services markets, from GOLD database

^{vi} <http://www.genome.gov/12513210>