Genomics – the future of healthcare and medicine

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Genomic medicine is becoming more mainstream and it is important that health professionals keep apace of this complex and rapidly developing field. This article provides an overview of genomics and the key role it will play in the management of medical conditions in the future.

The field of genetics has been recognised since the 19th century when Gregor Mendel studied his pea plants and discovered the fundamental laws of inheritance. But the term genomics was only coined in 1986, by the American geneticist Tom Roderick over a celebratory beer at a meeting about the mapping of the human genome. Genomics is now the accepted term for the study of the genome – the complete set of genes that encode for proteins, as well as the noncoding DNA in between – that exists in almost every healthy cell in the body. (An exception is red blood cells, which do not have a nucleus so have no DNA, and no genome.) Modern genomics studies the whole genome, the functions of genes and their interrelationships, and the technology that is needed to achieve this latter-day scientific breakthrough.

We used to be taught about the simple idea of one single gene being responsible for a characteristic, and faults in that gene causing illness. We now know it is a lot more complicated than that. There are around 4000 inherited diseases caused by single gene, or Mendelian, disorders. Examples we all recognise are cystic fibrosis, Huntington disease and sickle cell anaemia. But there is growing awareness of polygenic diseases, which are associated with several genes and influenced by environmental factors too. The noncoding DNA, which used to be thought of as junk, is now known to be far more important than we previously recognised.

Nature and nurture both matter in polygenic conditions; you may inherit a genetic predisposition to diabetes, but diet and lifestyle will influence whether and when you actually become diabetic. Cancer, diabetes and cardiovascular disease are all now recognised to be multifactorial and polygenic. Given the huge burden these three conditions place on individual sufferers and on healthcare provision, the race is on to use genomics to find novel solutions.

The Human Genome Project
The Human Genome Project (HGP) was an extraordinary, groundbreaking international research project completed in April 2003 (see Table 1). It took 13 years
and cost £2 billion. The HGP sequenced and mapped all of the genes that make up a human being, providing a complete genetic blueprint. The sequence is actually a composite derived from several individuals so it is a ‘representative’ or generic sequence. One use of the HGP is to look for genetic variations that increase risk of specific diseases, such as Alzheimer’s disease, or to look for the type of genetic mutations frequently seen in cancerous cells. Technological developments now mean that the human genome can be sequenced in a few days for under £1000. Home-based ‘spit tests’ now available commercially online can provide limited genetic information for under £125.5

**How does the genome work?**
The genome is one complete set of the genetic material in a cell.6 In humans, the genome is made up of around three billion nucleotide base pairs, which make up DNA molecules. Less than 2 per cent of the genome actually codes for proteins. The other 98 per cent is noncoding; some of the noncoding sequences regulate the transcription of proteins and some are transcribed to RNA but do not get translated into protein. It is a staggering fact that humans only have about 20,000 protein-coding genes – the same as a starfish. The function of the remaining noncoding DNA is not yet fully established, but it is thought that it may have a role in regulating and controlling gene expression.

**Why genomics is important now**
It is getting cheaper and faster to sequence the human genome. It took 13 years to first sequence it because the DNA sequence in humans is very long (three billion nucleotide base pairs) and the sequencing machines used to be very slow. Now, machines can sequence a human genome in days and the cost is falling rapidly. The technological advances have led to a giant leap forward in the scope of genomics and its growing role in healthcare and the pharmaceutical industry.

**How is data interpreted?**
Genomic data does not tell us much on its own. Clinical information about a person’s phenotype has to be considered alongside genomic information to make any sense of the raw data. Phenotypic information includes symptoms, age of onset and physiological measurements like blood pressure. Past medical history and medications also need to be factored in.

**What is personalised medicine?**
One day, perhaps quite soon, we will look back on the days when we prescribed the same treatment to everyone with a given condition as unbelievably crude. The holy grail is to tailor treatment to the individual, using genomic data about them and their disease.

Your genomic data may be used to predict which treatment option is likely to be most effective for you and how you are likely to respond. The example most widely quoted is women with HER2-positive breast cancer. Human epidermal growth factor receptors (HER) are proteins embedded in the cell membrane that communicate signals that turn genes in the cell on and off. Some types of breast cancer have overexpression of HER2 that allows cancer cells to proliferate. The drug trastuzumab (Herceptin)6 is a monoclonal antibody that blocks HER2 receptors and slows cancer growth. It is only effective if you are HER2-positive, so the treatment is tailored to the molecular type of cancer.

Genomics can find the small subgroup of people with type 1 diabetes who can be managed on oral medication rather than insulin.8 It can predict and track outbreaks of infectious diseases by analysing the genome of the responsible microbe. It can also allow people to take preventive action if they find they carry a genetic mutation that increases their risk of developing disease. Actor Angelina Jolie stimulated a lot of interest and debate when she underwent prophylactic bilateral mastectomy and oophorectomy after discovering she carries a BRCA1 gene mutation.10

There is still a lot of work to be done. The hope is that genomics will allow faster and more accurate diagnosis, treatments and the potential to cure diseases that currently have a poor prognosis.

**Use of genomics in medicine**

**Cancer**
Testing both the patient’s own genetic makeup (‘germline’ DNA) and the tumour DNA (‘somatic’ testing) are important in diagnosing and treating inherited cancers.11 Only around 5 per cent of cancers are due to familial cancer syndromes such as breast or ovarian cancer, associated with mutations in the BRCA1 and BRCA2 genes. Testing allows members of these families to identify whether they are at increased risk and offers them options. Some may choose to do nothing, others will opt for increased screening or preventive surgery. Carriers of a gene mutation may opt for assisted reproduction (IVF) with preimplantation testing of embryos12 so that only unaffected embryos are used. This may sound a bit like eugenics to some, but in families that have been blighted by early cancer deaths for generations, these techniques offer a chance to eradicate further cases in future offspring. Some ethicists argue that once this chance to spare future offspring undue suffering exists, it is immoral not to use it.

**Infectious diseases**
Genomics is set to transform the way we diagnose and treat infectious diseases within the next five years.13 If we have a patient with tuberculosis, sequencing the genome of the microbe will be used to predict which antimicrobials are most likely to work. In public health, genomic information will allow tracking and planning of strate-
ries to combat potential epidemics like swine flu and Zika. Public Health England has already used whole genome sequencing to track Salmonella outbreaks.14

Rare diseases

Rare diseases are not that rare overall – they affect about 7 per cent of the population and are usually inherited, in over 80 per cent of cases.15 Detailed molecular diagnosis is important to allow proper management and follow-up as well as alerting other family members. Examples include cystic fibrosis, Huntington disease, some rare childhood cancers and polycystic kidney disease. The 100,000 Genomes Project is recruiting people with rare genetic disease who do not have a molecular diagnosis yet.16

Common complex diseases

All aspects of health – good and bad – are a combination of genetic and environmental factors. Genetic profiling will identify susceptible individuals so that they can have screening and lifestyle advice tailored to their higher than average risk. This may be particularly useful in the case of prostate and breast cancer as well as common conditions like diabetes.17

Many people do not know much about their family history – they may be adopted, have lost touch or family members may have died prematurely from other causes. Genomic profiling will give people a more accurate way of knowing whether they are at risk of common conditions. This carries its own problems: anxiety, the need to tell family members who may prefer not to know, the duty to inform insurance companies and distress if further screening or intervention is recommended but not available on the NHS.

The 100,000 Genomes Project

The 100,000 Genomes Project, delivered by Genomics England,16 is an ambitious project that aims to sequence 100,000 whole genomes from 70,000 people who have either common cancers or rare inherited diseases, together with their families. The NHS is particularly well placed to carry out this work. It holds information on UK citizens’ medical history and can link it with their genomic data. This is vital in trying to work out how our genetic blueprint actually plays out in real life; for example, an individual may be a BRCA1 mutation carrier but never develop breast or ovarian cancer. We need to understand why that is. Genomics England says it has invested in the latest, state-of-the-art sequencing machines to sequence the 100,000 genomes in the project: “This is the first time sequencing has been done on such a scale in the UK. At first, all results will be double checked using existing clinical testing. This is to ensure that the information it delivers is of such high quality that doctors are confident to use it in making major decisions about care.”

There is a lot of raw data that needs to be crunched. Just one genome’s data is about 200GB – the storage capacity of a typical laptop – and we still do not know what a lot of the genome codes for. So once Genomics England sequences 100,000 genomes, the next task is to try to tease out what the differences between a person’s genome and a reference genome actually mean. There may be millions of tiny variants and interpreting which ones are harmless variations between individuals and which are contributing to disease is a massive challenge. Once the significance of the variations is known, this will need to be interpreted clearly to clinicians and patients.

There are novel security issues involved in collecting and storing this data; people will need to feel confident that it will not end up in the wrong hands. An ethics board advises on tricky problems like consent, how participants get their results and exploitation of the data for commercial gain by innovative and pharmaceutical companies. Patients are explicitly asked if they are willing for commercial companies to be able to conduct approved research on their data. Genomics England says it is “developing ways of charging for its data services to ensure that the costs of maintaining the data are shared with companies and that the UK tax payer will benefit should companies successfully develop drugs, devices, treatments, diagnostic tests or other services through its use. If successful products are developed, it means that patients are benefitting.”

Pharmacogenetics and pharmacogenomics

The field of pharmacogenetics is the study of the genetic basis for the difference between individuals’ response to a given drug. We see this in clinical practice all the time; one patient may get a massive drop in blood pressure when prescribed an ACE inhibitor, another may barely respond to it. We assume a genetic basis for the response or lack of it, but we have no way of predicting which individuals will be affected.

Pharmacogenomics is a relatively recent branch of pharmacogenetics.19 It uses population genetic information to research, design and develop new drugs and explore the uses and dosage of these drugs in clinical practice. In time, it should pave the way to personalised medicine, which tailors drug prescribing to the genomic characteristics of an individual. Prescribing in the future will be less ‘one size fits all’ and more like a bespoke piece of tailoring.

The vision is that GPs will be able to offer point-of-care testing for genetic variants that predict the likely response to a drug. One example that may come on stream soon is the variant involved in statin-induced myopathy. People who have a variant of the gene that encodes for a hepatic carrier transporter can be predicted to have a high risk of myopathy associated with simvastatin use.19 Guidelines advise prescribing an alternative statin or lowering the dose in individuals who are likely not to metabolise simvastatin efficiently. You may say, why not just “suck it and see” as we do now and, in the case of drugs that only cause mild and reversible side-effects, our current empirical approach may seem reasonable. But it is clear that being able to predict response using genomics would be particularly valuable when the stakes are high; when adverse reactions can be irreversible or lethal.

Genomics England has already partnered with 10 pharma and biotech companies to develop new diagnostics and treatments for people with rare diseases and cancers, using the genomic sequences gathered through the 100,000 Genomes Project. The companies – including AbbVie, Alexion Pharmaceuticals, AstraZeneca, Biogen, GSK, Roche, Takeda and UCB – work
in a public-private partnership called the GENE Consortium to analyse DNA sequences and find new research targets. About a third of all new drugs in development are using genomic data.

Pharmacogenomics is evolving
Pharmacogenomics has come a long way in a short time. From 1957, phenotyping tests involved giving a person a probe drug, measuring the metabolite in the blood and calculating the metabolite to parent drug ratio. This gave a measure of how that individual metabolises a drug. This method is still in use in the NHS today. For instance, if you lack the enzyme that metabolises azathioprine, you are more likely to get accumulation of a toxic metabolite that causes a fall in white blood cells. One in 300 of the population are homozygous deficient in this enzyme and therefore more prone to azathioprine-related leucopenia. Phenotypic testing remains important even now that the molecular basis is known because there are several different gene mutations that can underlie the enzyme deficiency.

From 1990, the technique polymerase chain reaction (PCR) allowed amplification of a piece of DNA to produce millions of copies. This allowed researchers to look at individual genes and how they affect drug response. Professor Sir Munir Pirmohamed gives the example of abacavir, a drug for the treatment of HIV that causes hypersensitivity reactions in about 5–7 per cent of individuals. When you rechallenge a patient who has had a reaction, it can lead to a particularly severe reaction, which has led to deaths. A particular HLA allele, HLA-B*5701, was found to be associated with this hypersensitivity reaction. Since 2006, every NHS HIV clinic uses a HLA-B*5701 screening test using PCR before starting abacavir and rates of hypersensitivity reaction have fallen to less than 1 per cent.

The 21st century has seen the advent of genome-wide association studies (GWAS). Researchers compare single nucleotides within the DNA sequence that show high variability between individuals. These variations are called single-nucleotide polymorphisms (SNPs) and the technique uses fluorescent labels to display them. About half a million SNPs can be compared at any time. GWAS have shown that individuals with hepatitis C who have a particular polymorphism of the gene IL28B are more likely to respond to treatment with interferon alpha than those who do not.

Sequencing the genome is where we are heading. This has already had the most impact in the field of cancer. About half of all melanomas have mutations in the BRAF gene, which encodes for the enzyme B-Raf, involved in regulating cell growth. Two drugs, vemurafenib and dabrafenib, which inhibit the B-Raf enzyme, have been shown to halt the progression of the most advanced metastatic malignant melanomas, albeit temporarily. Both drugs have been approved by NICE for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma.

Where are the innovations?
New drug treatments based on genomic research are likely to take at least another decade to come to market. However, screening and diagnostic tests are becoming available, including DIY kits that can be bought online by members of the public (23andMe). The field of translational medicine seeks to translate laboratory breakthroughs to clinical and community settings as rapidly as possible.

Socialising the Genome
As GPs, we need to understand genomics so that we can explain it to our patients. Patients already come in to see us to discuss how their cancer treatment may be tailored to their genomic profile, for example women with breast cancer on trastuzumab. Increasingly, they may come in clutching the results of a DIY kit like 23andMe (see below). In the next few years, we are likely to prescribe treatments based on genomic data that will tell us which person with hypertension is likely to benefit from an ACE inhibitor and which from a calcium-channel blocker.

Socialising the Genome is a project from Genomics England that sets out to explain some of the complex concepts involved. It has produced short and

Table 1. Facts about the Human Genome Project

- In 1990, the National Institutes of Health (NIH) and the Department of Energy joined with international partners in a quest to sequence all three billion letters, or base pairs, in the human genome, which is the complete set of DNA in the human body. This concerted, public effort was the Human Genome Project
- The Human Genome Project’s goal was to provide researchers with powerful tools to understand the genetic factors in human disease, paving the way for new strategies for their diagnosis, treatment and prevention
- All data generated by the Human Genome Project were made freely and rapidly available on the Internet, serving to accelerate the pace of medical discovery around the globe
- In April 2003, researchers successfully completed the Human Genome Project, more than two years ahead of schedule.
- The Human Genome Project has already fuelled the discovery of more than 1,800 disease genes
- As a result of the Human Genome Project, today’s researchers can find a gene suspected of causing an inherited disease in a matter of days, rather than the years it took before the genome sequence was in hand
- There are now more than 2,000 genetic tests for human conditions. These tests enable patients to learn their genetic risks for disease and also help healthcare professionals to diagnose disease
- At least 350 biotechnology-based products resulting from the Human Genome Project are currently in clinical trials
- Much work still remains to be done. Despite many important genetic discoveries, the genetics of complex diseases such as heart disease are still far from clear
- Pharmacogenomic tests can already identify whether or not a breast cancer patient will respond to the drug trastuzumab, whether an AIDS patient should take the drug abacavir, and what the correct dose of warfarin should be

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engaging animated films that can be watched online.28 “We think everyone deserves to have a heads-up on what genomics is about,” they say.

DIY gene testing kits
A home-based gene testing kit called 23andMe is available online for £125.5 You need to register and fill in some information on the company’s website and spit into a tube that is sent to their laboratories in the post for analysis. In the USA, people can only get information about their ancestry, but in the UK and Europe, more detailed information, such as BRCA1 and BRCA2 status, is reported back via their website. Our patients will increasingly turn up to GP surgeries clutching the results and asking for referral to genetics counselling.

Consultant genetics counsellor Christine Patch from Guy’s and St Thomas’ Hospital, London has told me she has several areas of concern about self-testing: the limitations of the test, how commercial companies may exploit the data and whether NHS genetics counselling services will have the capacity to deal with the new referrals.29 Dr Katherine Leask, a medicolegal adviser with the Medical Defence Union,30 has said that doctors need to be aware of the challenges that increased use of kits like 23andMe will pose. “Genomic medicine is going to become more mainstream and doctors need to know what tests are available.”

This need to educate healthcare professionals in genomic medicine has been highlighted by Professor Ian Cumming, chief executive of Health Education England.31 “The genomic revolution is critical to the personalisation of healthcare, to the prediction of disease and to the prevention of disease. That’s why we will make sure we train not just our current workforce but our future workforce in the skills they need to be able to respond.” The future is genomics and, like it or not, we are part of it.

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Declaration of interests
None to declare.

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