GRESHAM COLLEGE

14 MARCH 2018

PERSONALISED MEDICINE: MADE FOR YOU

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Introduction

We are all human, but we are all different. As we have come to learn more about our genetic make-up, we have begun to understand better the causes of some of these differences, and to work out why individuals and groups of patients respond differently to both disease and treatment. One treatment does not fit all. This is the basic premise of personalised medicine.

The premise rests on the proposition that detailed knowledge of the genetic make-up of patients would allow the design or selection of treatments suitable for particular sub-groups of patients and establish when was the best time to give that treatment. The therapy would be 'targeted' at the appropriate audience. It is only rarely targeted to the *individual*. At least not yet.

There has been a great deal of hype about personalised medicine, similar in some ways to the space race of the 1960's (indeed Obama, Biden and MD Anderson have likened the field to a moonshot). Yet it is salutary to remember, as Rose has pointed out[1], that almost all the major advances in human health have come from interventions that have been anything but personal. Clean water, effective sewage systems, regulation of food safety, controls on environmental pollutants, together with population-wide programmes of vaccination, maternity services and similar measures are effective precisely because they address the underpinnings of ill health *without* differentiating individuals. Rose also points out that it was this population-based view of medicine and social insurance that formed the basis of Beveridge's construct for the NHS. *Impersonalisation*, counter-intuitively, was the route to health for all. The hype surrounding personalised medicine has led to a belief that change will be rapid and so medicine will be disrupted and quickly. But in a 2010 survey of involved life scientists published in Nature*, more than 30% of respondents thought that it would take at least 10-20 years to become common place, 25% thought it would take much longer and 5% didn't expect it to happen 'within their lifetime'. We are in the middle of this change.

In this lecture and essay I will describe the basic principles of personalised medicine and then turn to the data, analytic, economic and ethical challenges which have emerged.

Definitions

So, what do we mean by PERSONALISED MEDICINE? The term is now used widely in healthcare and the media, but it means different (sometimes very different) things to different people.

The term emerged after the Human Genome Project began in 1990 (https://www.genome.gov/12011238/an-overview-of-the-human-genome-project/). This project exposed the fact that some apparently well understood and comprehensive diagnoses were, in fact, composed of many genetic variants, and that drugs previously thought to have uniform effectiveness in that disease proved ineffective in some of those genetic variants.

* http://www.nature.com/news/2010/100623/pdf/4651000a.pdf

We started to understand that the genetic footprint of a patient (**THE GENOTYPE**) might also influence both susceptibility to disease (potentially allowing us to understand how to prevent particular diseases) and the long-term response to treatment. Leroy Hood predicted in 1992[2] that the learning from the Human Genome Project would '*transform the way we deal with disease*'. In fact, as is the case in much of medicine, it has proved much more complex than first thought.

Redekop and Mladsi identified[3] three example definitions of personalised medicine:

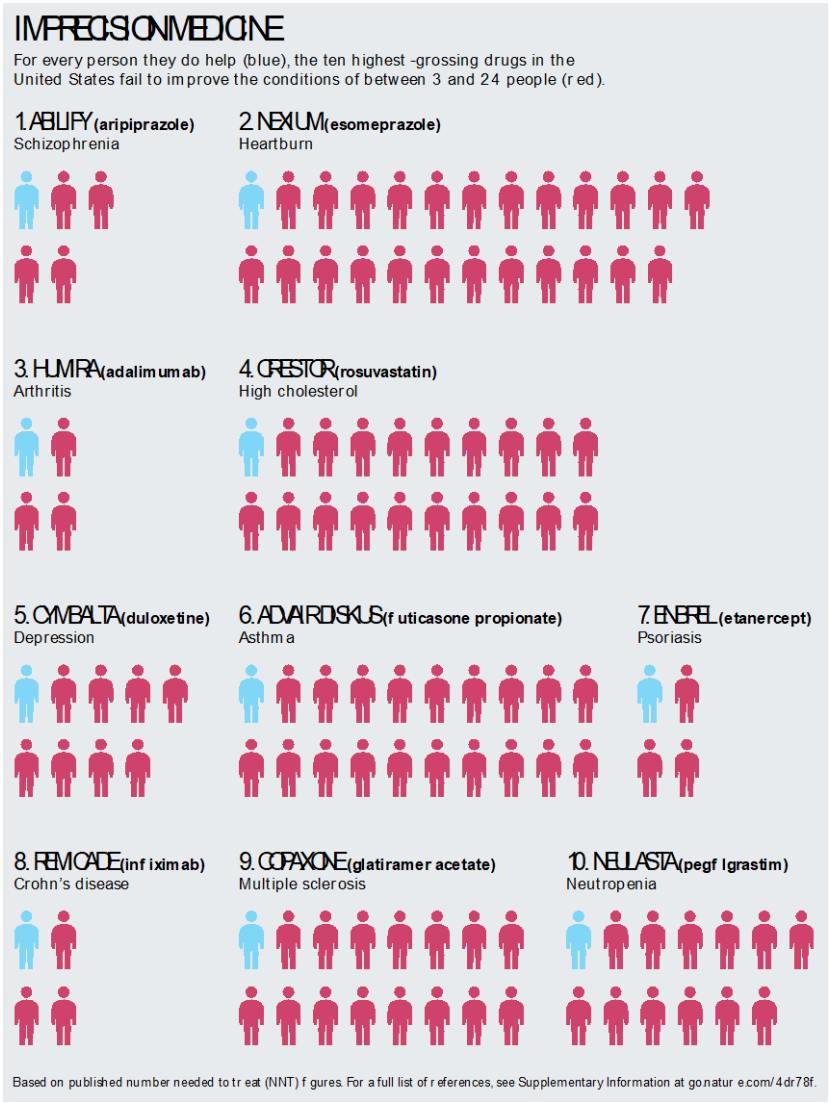
> 1. "a medical model that proposes the customization of healthcare, with decisions and practices being tailored to the individual patient by use of genetic or other information."
> 2. "the tailoring of medical treatment to the specific characteristics of each patient. [It] does not literally mean the creation of drugs or medical devices that are unique to a patient. Rather, it involves the ability to classify individuals into subpopulations that are uniquely or disproportionately susceptible to a particular disease or responsive to a specific treatment."
> 3. "a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease."

In addition to the genetic information about the patient, it is necessary to collate the maximum amount of information about each patient and their biochemical make-up to provide the best chance of defining a treatment 'suitable for just them'. This holistic description of a patient's state or disease, other than genetic information, is called **THE PHENOTYPE.** This term too has multiple definitions, but perhaps the most comprehensive is this[4];

> "the collection of noticeable properties of an organism, representing its physiology, its morphology at different levels, including cellular, tissue, organ, and body levels, and its behaviour, incorporating even features such as the gene transcription in response to environmental factors."

It is salutary to note that many drugs which are designed to treat certain conditions or act in a certain way prove ineffective in certain individuals. It can be difficult to predict who will benefit from a medication, who will not respond at all, and who will experience negative side effects (called adverse drug reactions)[5]. In 2003, Allen Roses, then world-wide vice-president of genetics at GlaxoSmithKline pointed out that >90% of drugs only work in 30-50% of patients for whom they are prescribed[†]. Nicholas Schork pointed out[6] in a recent article in Nature that the top ten highest grossing drugs in the United States helped only between 1 in 25 and one 1 in 4 of the people who take them[‡]. Trial data had suggested that they should work in that *population* of patients, but they proved not to work in many *individual* patients. See panel below (from Shork's paper) headed *Imprecision* Medicine.

[†] http://www.independent.co.uk/news/science/glaxo-chief-our-drugs-do-not-work-on-most-patients-5508670.html
[‡] The panel "Imprecision Medicine' was clearly created for dramatic effect and follow up in some of the background studies is short. There may well be more to it!



At least in part, this lack of uniform response is due to the varied genomic make-up of the patients involved. The study of the relationships between the underlying genetic make-up of a patient and their response to drugs has become known as **PHARMACO-GENOMICS.** Identifying which drug will work in a particular patient, and also those in whom a drug might cause harm, are key targets of personalised medicine. For example, analysis of genotypes of the enzyme thiopurine *S*-methyltransferase has helped clinicians predict drug toxicity in patients that require treatment with the drugs azathioprine or 6-mercaptopurine, important therapies for immune disorders and acute lymphoblastic leukaemia (ALL) respectively.

Personalised medicine does not *literally* mean the creation of drugs and devices specific to an individual patient, rather the classification of patients into smaller and smaller populations with identical conditions who are likely to respond in a particular way. In business, this might be called segmentation of the market or customer base. One useful way to think of personalised medicine is as the science of **TARGETED** therapy; getting the right treatment to the right patient at the right time.

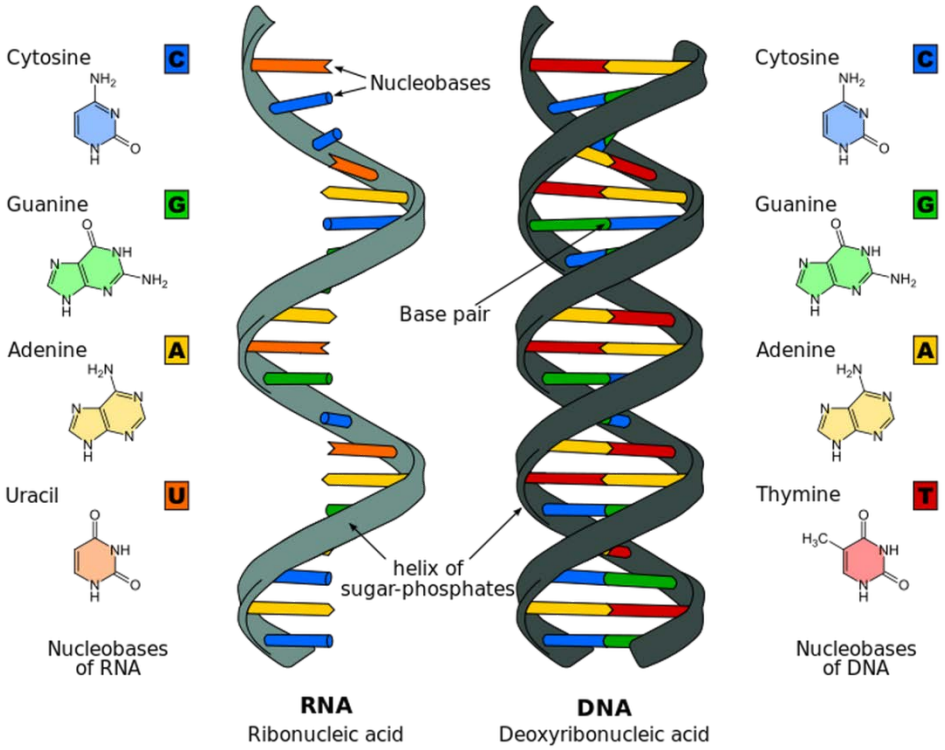
Personalised medicine has always been around (in the sense that doctors deal with individual patients), and our greater knowledge has simply allowed us to have a better chance of making it truly specific. It is for this reason that many prefer the term **PRECISION MEDICINE**. Precision medicine aims to use state-of-the-art genomic technologies, rich medical record data, tissue and blood banks (to provide detailed diagnostic and bio-marker information accurately to describe the phenotype of the patient) and clinical knowledge that will allow clinicians to tailor treatments to groups of individuals, thereby greatly reducing the costs of ineffective therapies incurred through the current trial and error clinical model. Professor Sir John Bell and the Academy of Medical Sciences (in an excellent report[7]) have preferred the term **STRATIFIED MEDICINE,** but essentially it incorporates the same fields.

Professor Bob Sade of Charleston, SC, USA drew my attention to the general division of people's ideas into **'lumpers'** and '**splitters'**. In the time of Hippocrates, a splitter, everyone was considered an individual, wholly different from his peers, and his medicine was based on the concept of an imbalance of the humours, specific to the individual. By the time of Thomas Sydenham in the 17th Century, observation and science in medicine (led by Harvey and Versalius) had laid the ground for 'species' of diseases, lumping symptoms together as diseases. As Sade further highlights, we are now splitting again, creating one long historical cycle over the last 2500 years.

A Bit More About the Genome and the Genotype

What is the genome, and how is it obtained? A genome is all the genetic information of an organism. Wikipedia sometimes comes up with an excellent and simple description of a complex idea…necessary for a surgeon like me. They describe the human genome is analogous to the instructions stored in a cookbook. Just as a cookbook gives the instructions needed to make a range of meals from a holiday feast to a summer picnic, the human genome contains all the instructions needed to make the full range of human cell types, as well as controlling a substantial proportion of a wide range of behaviours and attitudes.

- The book (genome) would contain 2 x 23 chapters (chromosomes);
- Each chapter contains 48 to 250 million letters (A[denine],C[ytosine],G[uanine],T[hymine]) without spaces;
- Hence, the book contains over 3.2 billion letters total;
- The book contains approximately 20,000 different recipes (genes), which together make up less than 2% of the letters in the book[§]. [**]
- The book fits into a cell nucleus the size of a pinpoint;



DNA sequencing is the process of determining the precise order of nucleotides within a DNA molecule. It is used to determine the order of the four bases—adenine, guanine, cytosine, and thymine (AGCT)—in a strand of

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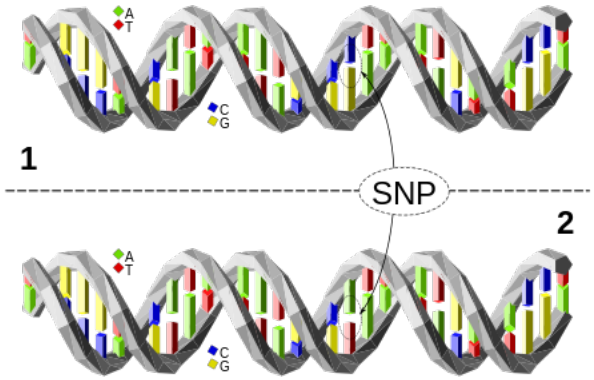
§ The rest of the letters are called the **non-coding region** of the genome and we are only now beginning to understand how these letters regulate the expression of the genome in cells and in the whole individual: "adding flavour to the recipes"

** Vanya Loroch considers that the genome is not just one giant 'cookbook', but rather a collection of 2x23 cookbooks that contain recipes (i.e. some 20,000 coding genes, only 1.5% of the genome and the 'rest' 98.5% of the genome) http://www.biolink.express/demos/genetics/story.html

DNA. The advent of **rapid DNA sequencing** methods has greatly accelerated biological and medical research and discovery. Sequencing is a highly technical, increasingly automated and competitive field. Much progress has been made, reducing the cost of whole genome sequencing dramatically over recent years. At the turn of the century, the cost was approximately $100 million dollars per genome analysis, but now, with **next generation sequencing** it has fallen to less than $1000 dollars per genome[8], and this has also reduced to days the amount of time it takes to perform an analysis. There are clear parallels with Moore's law relating to processor speed.

Single nucleotide polymorphisms, frequently called **SNPs (pronounced "snips")**, are the most common type of genetic variation among people[5] (https://ghr.nlm.nih.gov) . Each SNP represents a difference in a single DNA nucleotide. For example, a SNP may replace the nucleotide cytosine (C) with the nucleotide thymine (T) in a certain stretch of DNA.



SNPs occur normally throughout a person's DNA. They occur once in every 300 nucleotides on average, which means there are roughly 10 million SNPs in the human genome. Most commonly, these variations are found in the DNA *between* genes. They can act as biological markers, helping locate genes that are associated with disease. When SNPs occur within a gene or in a regulatory region near a gene, they may play a more direct role in disease by affecting the gene's function.

Whilst most SNPs have no effect on health or development, some have proven to be very important in the study of human health. Some may help predict an individual's response to certain drugs, susceptibility to environmental factors such as toxins, and risk of developing particular diseases. SNPs can also be used to track the inheritance of disease genes within families.

Researchers have pooled their efforts to identify common genetic variations in humans and have made the data freely available to researchers worldwide via the International HapMap Project (Hap stands for haplotype) (https://www.genome.gov/10001688/). This allows individual genomic data to be compared with the data available on a huge database, looking for information that will predict an individual's susceptibility to disease or potential response to therapy. In this decade, a patient's genotype is only analysed in a few centres and in association with a few diagnoses and potential treatments. This is most effectively being undertaken in the Vanderbilt (Nashville, TN, USA) "PheWAS" database (https://phewascatalog.org). But the cost, the speeds of analysis and the rapidity of data analysis are all expected to continue to fall, hugely expanding the potential use of this technology in the years to come.

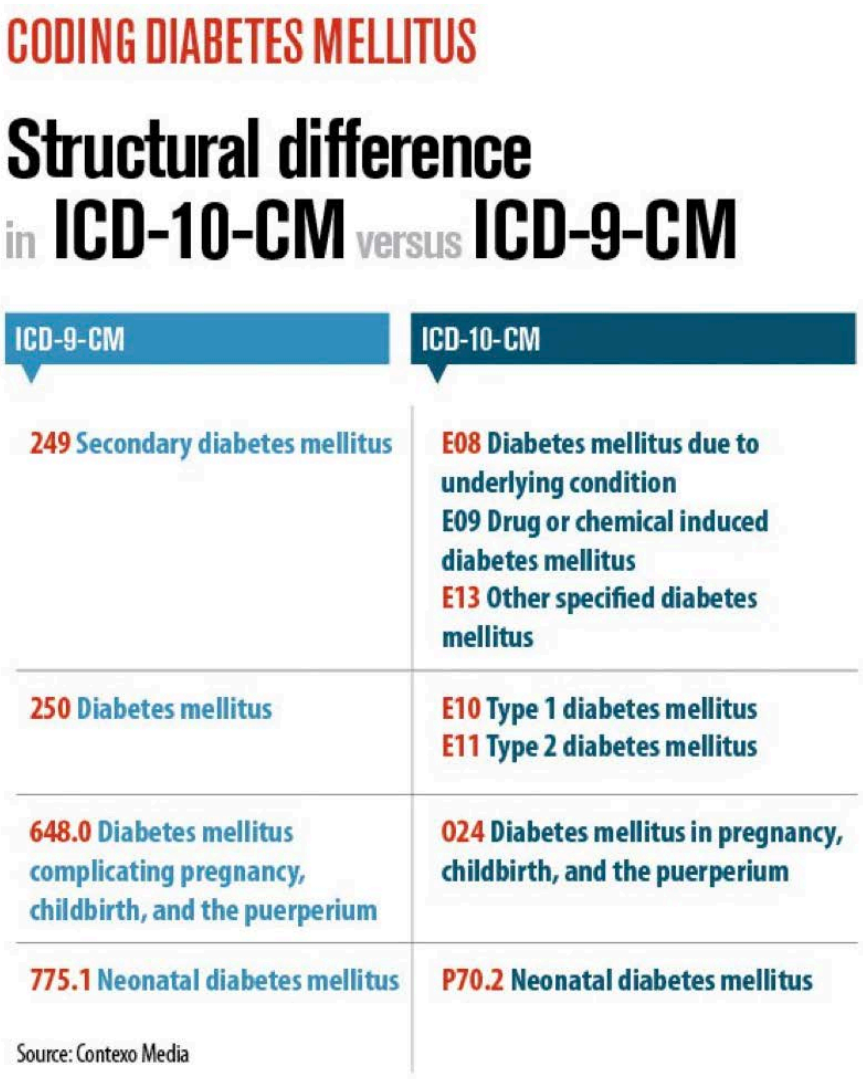
Indeed, this is already happening (Winlaw, D. *Personal Communication*). HapMap was more relevant in the days of genome-wide association studies (GWAS) when we looked for a relationship between common SNPs and common diseases. Low statistical power meant thousands of patients and controls were required for each study and an additional replication cohort was usually required.

Unfortunately, GWAS have not yielded the clinically actionable information we were hoping for – the expectation that a common disease is associated with a common SNP. This issue, and the development of massive parallel sequencing (exomes and now genomes) have brought the focus of gene:disease relationships back to individuals and families. We don't need only to sequence SNPs on a chip, because now we can sequence the whole genome. This is another driver of both personalised and precision medicine.

What Do We Call Diseases?

It is more complex than we first thought; a new **taxonomy** is developing.

We have named and then classified disease throughout the history of medicine. But the most commonly used classification evolved from the work of the French statistician Jacques Bertillon (1851-1922). Between 1891 and 1893 he chaired a committee that introduced the 'Bertillon Classification of Causes of Death', the precursor of the International Statistical Classification of Diseases, known as ICD which continues to be published at intervals by the WHO (http://www.who.int/classifications/icd/en/). These classifications are based on descriptions of diseases which we have come to understand over several years. Each iteration refines the classification, as can be seen in this next panel looking at the changes to the classification of diabetes between ICD-9 and ICD-10. But since the advent of genotyping and matching those data with the phenotype, the complexity of diagnosis has increased dramatically. If we just look at Type 1 diabetes (E10 in ICD-10, absent in ICD-9), this complexity is evident.



Type 1 diabetes includes latent autoimmune diabetes in adults (LADA), Maturity onset diabetes of the Young (MODY) and neonatal diabetes mellitus (NDM). If we subdivide those with MODY based on the genotype and on the genotype/phenotype map (OMIM [online Mendelian inheritance in man] https://www.omim.org) the table looks quite different††;

Type 1 Diabetes

†† I am grateful to Vanya Loroch for this table www.loroch.ch

Type	OMIM	Gene/protein
MODY 1	125850	hepatocyte nuclear factor 4α
MODY 2	125851	glucokinase
MODY3	600496	hepatocyte nuclear factor 1α
MODY 4	606392	inulin promoter factor-1
MODY 5	137920	hepatic nuclear factor 1β
MODY 6	606394	neurogenic differential 1
MODY 7	610508	Kruppel-like factor 11
MODY 8	609812	Bile salt dependent lipase
MODY 9	612225	PAX4
MODY 10	613370	INS
MODY 11	613370	BLK
Permanent neonatal DM	606176	KCNJ11 and ABCC8
Transient neonatal DM	601410,610374, 610582	ABCC8

What it means is of course for the experts (although the idea that we may understand more about insulin resistant diabetes and identify new drug targets is really exciting)! But it is the growing complexity of diagnosis and its taxonomy that I want to get over to you. The sheer number of diagnoses which can accumulate for an individual expressed in a combination of genetic and phenotypic terms is potentially huge, let alone the detailed genetic sequencing information.

But it is important; only this month (1st March 2018), researchers in Scandinavia demostrated[9] (https://doi.org/10.1016/S2213-8587(18)30051-2) that the now classic divisions of Type 1 and Type 2 diabetes were insufficient to describe the detail of disease. Using a large dataset of patients and analysing many aspects of the *phenotype* of the disease, they identified five replicable clusters of patients with different patient characteristics and different risk of diabetic complications. The authors argue that if patients could be allocated to the correct diagnostic 'cluster', this would help tailor therapy and be a 'first step towards precision medicine in diabetes'.

Thomas and his colleagues in Exeter[10] used data from the UK Biobank to reveal that genetic susceptibility to type 1 diabetes results in non-obesity-related, insulin-dependent diabetes presenting throughout the first six decades of life, despite it being thought primarily to occur in the under 30's. As patients age, the prevalence of Type 2 diabetes increases, and so it is highly likely that many patients with Type 1 diabetes presenting *after* age 30 are at great risk of inaccurate diagnosis and thus receiving inappropriate advice or treatment, making them more likely to become insulin dependent or develop serious complications. Accurate phenotypic and increasingly genetic diagnosis is becoming essential.

We are probably more familiar with the classification of disease using genetic classifications in the context of cancer, for example. The drug imatinib was found to double survival rates of leukaemia patients who had a chromosomal abnormality in their tumours called the Philadelphia translocation. And cetuximab improves the survival of people with colorectal cancer whose tumour cells carry a mutated *EGFR* gene but not a mutated *KRAS* gene[1].

You may have heard of the BRCA 1 and BRCA 2 genes[#] in the context of breast and ovarian cancer. Mutations in these genes can result in either failure of production of the repair proteins or mal-function of the proteins. Specific mutations are associated with a notable increase in risk of breast and ovarian cancer, and the mutation can be inherited. Hence some people (like Angelina Jolie) opting to have elective mastectomy based on a strong family history and confirmation of the gene mutation. Unfortunately, over 500 mutations of the BRCA1 gene have already been identified (https://commons.wikimedia.org/wiki/File:Mutations_on_BRCA1.jpg), further emphasising the complexity.

Genome-Wide Association Studies (GWAS) in my field of cardiovascular medicine have been largely disappointing, but an example of a big impact of genomics is illustrated by the PCSK9 story[11]. Helen Hobbs and Jonathan Cohen identified individuals with very low blood cholesterol levels (potentially protective against cardiovascular disease) despite having made no lifestyle adjustments; these people were considered extreme outliers. Hobbs and Cohen identified that such individuals had a 'loss of function' mutation in the gene PCSK9 which resulted in a low LDL (low-density lipoprotein) cholesterol[§§]. This discovery lead to the development of PCSK9 antibodies which are now being used to treat patients with statin-resistant hypercholesterolaemia. It has taken a remarkably short time to get from lab to clinic.

Partly as a result of this success, industry is now investing heavily in identifying outliers or "Black Swan" events. In oncology, Professor Raj Chopra of the Institute of Cancer Research, London calls these "elite responders"; a much more attractive term! This field of study is rapidly growing both in importance and rate of progress, as for example in relation to lung cancer and epidermal growth factor receptor (EGFR)[12].

These examples demonstrate that traditional diagnoses such as breast cancer or diabetes are too simplistic. They provide a useful linguistic shorthand to describe common diseases. An envelope perhaps with an address on it is a useful analogy. The country (UK) might represent say diabetes; the city (London) Type 1 diabetes; the postcode might describe the phenotype (insulin dependent) but the house number and name could contain greater detail of genetic information, relevant to you. And there may be more information to discover inside the envelope. The **taxonomies** of both disease and genetics have become very important.

Thus, a modern taxonomy would describe and define diseases based on their intrinsic biology, as well as their traditional 'signs and symptoms'. It would be linked to a deeper understanding of disease mechanisms and treatments. It would be dynamic, since information about disease grows at a remarkable rate. It should be publicly available so that researchers all over the world can use the same language. It has been described[13***] as the basis for a **knowledge network** or **an information commons.** It is self-evident that the **datasets** associated with such research, both in terms of patient phenotypic data and genetic information are enormous. And then we have to consider biomarkers.

Biomarkers

Markers of the state of disease

A biomarker is a biological marker and refers to a broad group of medical signs; objective indications of medical state which can be measured accurately and reproducibly[14]. As usual with these things, multiple

[#] BRCA1 and BRCA2 are tumour suppressor genes and play a vital role in the response to cellular damage through activation of specific DNA repair processes. When these genes are mutated, affected females are predisposed to breast and ovarian cancer and males to prostate cancer. The cancer cells become dependent on parallel DNA repair enzymes called PARP [Poly(ADP-ribose) polymerases] for survival. Inhibiting PARP with small molecule inhibitors results in cell death. PARP inhibitors such as olaparib are making a big impact particularly in combination, to the survival of women with BRCA mutant Breast and ovarian cancer. This synthetic lethal approach to personalised medicine is being used to discover new drugs, particularly where loss of tumour suppressor genes has been identified as drivers of cancer

[§§] The PCSK9 protein competes with LDL for the LDL receptor on the surface of gut and liver cells. High PCSK9 results in LDL receptors being blocked and inability to take up LDL for degradation in the liver (a genotype/phenotype relationship) and low PCSK9 (or loss of function) results in increased LDL receptors and low circulating LDL cholesterol.

[***] (https://www.ncbi.nlm.nih.gov/books/NBK92144/)

definitions exist, but this from the WHO seems to me to best capture the flavour of what they are; "*any substance, structure or process that can be measured in the body or its products and influence or predict the incidence or outcome of disease".*

Biomarkers are largely independent of how the patient feels and their sense of well-being and are not a substitute for clear end-points such as death or stroke. Well-researched and chosen biomarkers relate to the process and progress of a disease and can be measured at regular intervals to reflect both. They must thus be both *relevant* and *valid.*

We have all been made aware of the association between a high blood cholesterol level and the risk of coronary heart disease and heart attack. It is also well known that statins lower cholesterol levels in many people, and thus are said to reduce the cardiovascular risk. Blood cholesterol is a biomarker of the disease, and the drug's effectiveness can be measured by its ability to lower the levels of that biomarker. It is not always that simple. For example, a large and well-publicized trial of the combination of two cholesterol-lowering drugs, ezetimibe and simvastatin, highlighted the risk of relying too much on biomarkers[15]: although the combination treatment lowered subjects' cholesterol levels more than simvastatin alone, it did not lead to any improvement in atherosclerosis or overall mortality, calling into question a great deal previous research that depended on the assumption that lowering cholesterol necessarily lowered morbidity and mortality.

Bioinformatics

Managing the enormous amount of data

It will be obvious to the reader by now that there are significant data challenges associated with these developments. The amount of data associated with genome analysis is huge, but nothing compared to the complexity of the phenotype, multiplied by the years of exposure to environmental change during follow up, and the associated accumulation of biomarker data. Computers and 'big data' analytics are crucial to the exploitation of this burgeoning knowledge. But many challenges arise because of that.

We have already established that the development of personalised medicine is dependent on collecting, storing and analysing masses of data from both individual and populations of patients. Sharing that knowledge is a pre-requisite for personalised medicine. As a national service, the NHS is theoretically the ideal organisational framework to create such integrated and useful datasets‡‡. But as Armstrong[16] and others highlight, we must first overcome issues with patient trust, security and technology.

There have already been several high-profile data breaches in the UK. It was reported in 2017 that 26 million GP records had been made available to strangers[17]; the information commissioner's office (ICO) fined an HIV clinic £180,000 after it released data on 781 of its patients‡‡ and the WannaCry ransomware cyberattack shut down NHS computers across the country in May 2017 (see the excellent lecture by Martyn Thomas and Harold Thimbleby "Computer Bugs in Hospitals; A New Killer" given at Gresham College http://bit.ly/2oJRMOZ) .

In July 2017, the information commissioner found that The Royal Free Hospital did not comply with the Data Protection Act when it supplied the medical data of around 1.6 million patients to Google Deep Mind. The project they were working on was, however, really important for patients; using 'big data' techniques they were able to identify methods of early detection of renal failure in hospital patients from information routinely being collected by the hospital systems. It has also proved effective. Perhaps good has trumped evil, and perhaps both the Royal Free and Google are to be trusted in this context. But the media response suggested that trust was broken, and the publicity was damaging for data usage in healthcare. As the Information Commissioner , Elizabeth Denham, was quoted as saying[16] "*the price of innovation didn't need to be the erosion of legally ensured fundamental privacy rights".* Patient data are critical to progress, but we must ensure they are safe, auditable and not used for purposes to which the data donors did not consent.

‡‡ Jeremy Hunt, the Secretary of State for Health and Social Care, indicated in a 2015 speech that all patient and care records will be digital, real time and interoperable by 2020. Independent views suggest this is more likely to be 2027

‡‡ BBC. NHS trust fined for 56 Dean Street HIV status leak. May 2017. www.bbc.co.uk/news/ technology-36247186.

In my own experience of working with International Registries of patient data about congenital heart disease, I have observed that patients really do understand how important their own individual data is to 'the common good'. Withholding consent is as rare as rocking horse manure, but we are trusted to care for their data and to use them for that common good. Using data for commercial purposes, or as part of a 'Big Brother' state approach, is not acceptable to most, and the newspapers are right to challenge how the data are used. For an excellent review of the issues involved in big data, consent and anonymization see Mostert et al[18].

There are considerable obstacles in the way of getting these data to work for us. The availability and cost of computational biology and a socialised process for funding and sharing data (including if necessary with commercial entities) are rate limiting steps. The NHS would be an ideal organisation in which to do this, but the inability to standardise electronic patient records across the country and lack of political will (and perhaps imagination) have made and will make this difficult.

BIOBANKS are an extension of data collection. These are organised collections of biological material (including tissue) **and** the associated data[6]. Unfortunately, they have grown up in a rather haphazard way, with varying aims, governance, ownership and structure. Regulatory frameworks are gradually catching up with them, but the need for rigorous privacy rules is evident. In 1998 in Iceland, a Health Sector Database created a biobank and licensed it to a private company, deCODE. This relationship between public interest and a profit-oriented company sparked much controversy and remains a concern at the heart of anxieties about precision medicine, since much of the technical progress is in the hands of the private sector.

The NHS has established the 100,000 genomes project, which NHS England describes as ground-breaking and world leading[§§§]. This project builds partnerships between academia and the private sector to decode the genome in rare diseases and in cancer. Thirteen genomics medicine centres have been established in England to establish a full genomic medicine pathway. These centres aim to encourage and facilitate the participation of patients and family members (with their informed consent); collect samples to extract DNA; capture clinical information to inform the interpretation of the genome sequence; and establish the infrastructure to make genomic medicine a routine part of NHS care. Better media handling has made this particular public-private partnership less controversial. The potential benefits have been made clear. But…

We have all become rather used to the erosion of our 'private space' with regard to data. Most of us freely tick the 'Terms and Conditions' 'agree' box which IT companies present to us with every update, usually without ever reading the contents. We just want what the software offers and don't want to waste time on the legalese of the document. Very often buried in those T's & C's are statements describing what the company can do with your data. We are used to rigorous security screening of much of our personal data at airports, to giving our fingerprints to Homeland Security and to extensive video and GPS surveillance. Indeed, we are quite blasé about it. But our medical data are different, and our genetic information even more so. We read regularly about 'identity theft' but what more perfect definition of identity than your personal genome? I for one do not want that hacked by Russia or some teenage geek in his bedroom.

The data we collect by integrating biological and clinical datasets will be of immense value not just in treating but also in preventing disease by focussed public health interventions. That value must not be lost by further breaches of trust. The technical details of how datasets can be integrated and protected are beyond both the scope of this lecture and my experience, but are discussed by Fernald[8] and in the lecture by Thomas and Thimbleby (http://bit.ly/2oJRMOZ). Overby and Tarczy-Hornoch[19] give practical examples of what is needed in translational bio-informatics to minimise the risk of security breaches both by process and technology. A further excellent article about the relationship between data privacy and data confidentiality debate is provided by Lobato de Faria and Cordiero[20], in which they argue the need for continued development of the legal and regulatory framework within which health data exists to cope with the rapid progress in bioinformatics.

Targeted Therapies

The individual or groups of patients?

[§§§] https://www.england.nhs.uk/healthcare-science/personalisedmedicine/

When I hear discussion about targeted therapy or personalised medicine, I am always surprised that so many people believe that it really is targeted to the individual. As Rose describes[1], "*the genomic information allows the population to be divided into groups with different* ***probabilities*** *of responding to particular types of medication or developing an adverse reaction—one group has a high probability, another a lower probability, but for neither group is there certainty.*" He draws attention to the field of psychiatry as one which would benefit from improved rationality in the choice of drugs for depression. There are over a dozen agents to choose from, and they turn out to have different efficacy and different side effects in different patients. Only trial and error can be used to guide the physician's choices. We are a long way from having enough genetic/phenotypic correlations to be able to achieve the precision we seek. There are also important issues to consider in how we carry out research studies[6], since by definition the number of patients in each group must fall as precision increases. Discovering that an intervention works well in certain groups currently happens relatively rarely, and often by chance. Researchers typically get disappointing results with a drug in large, population-based trials. This leads them to conduct *ad hoc* post-trial analyses, in an attempt to identify the factors that cause some of the people in the trial to seem to be responsive.

Schork[6] rightly describes this approach to discovery as 'inefficient at best', and goes on to say

> "*Conventional phase III trials involve thousands of people. The intervention being tested is often given at random to one group while another group receives a sham treatment, such as a sugar pill or the standard treatment that physicians would give such patients. Because scant data are collected on factors such as genetics, lifestyles and diets, the results of these trials often indicate the need for yet another study to validate the effectiveness of the intervention among the apparent responders and to establish the underlying mechanisms.*"

As a result, researchers have suggested trial design modifications such as 'basket' trials, 'umbrella' trials, and 'n of 1' trials. Again, I do not have time or space to go into these in any detail, but they are designed to collect a great deal of relevant information from **each** person, selected on the basis of genetic susceptibility, as frequently as possible over the course of treatment. Drugs could then be changed in that individual and the assessment repeated, gradually determining (using biomarkers) which drug works best for them or patients like them. They are not locked in to receiving therapy which proves useless to them. These trials are very appropriate for early stage assessment of new therapies in genetically similar people or diseases before moving on to large scale even more expensive trials.

You could reasonably argue that every treatment for disease should be given in this way; each individual providing data for the common good about what worked well for them. This targeted approach is very popular with patient groups representing those with rare genetic diseases; they are often eager to be involved in the testing of candidate drugs[6]. Sadly, it seems basket and umbrella trials have not yet made a significant impact of survival in patients, at least those with cancer[21].

We do clearly need to be more focussed in our delivery of drugs if the observations summarised in the panel 'Imprecision Medicine' above are reproducible. Not only is it wrong to give medication to someone for whom it will not work, but also to expose them to potential side effects. Further, it must add up to a huge amount of wasted money and product, which is clearly unacceptable given the current costs of healthcare.

Patient-Specific Treatment

Treatment for one patient

An example of much more patient-specific treatment is **CAR-T** therapy, which has huge promise in many (especially haematologic) malignancies. CAR-T stands for **chimeric antigen receptor T-cell therapy.** The CAR-T strategy involves removing a patient's own CD8+ T cells (these are also known as killer T-cells; the CD8 protein on their cell surface allows them to bind to and to kill specific cells that they recognise), re-engineering them to recognise specific tumour antigens and then putting them back into the patient as so called "living drugs." The clinical outcomes have been extraordinary and whilst not curative, treatment has transformed many terminally ill patients in a way that no one dared hope for. It is likely to be the hottest topic in oncology for probably the next two decades at least (Acton, G *Personal Communication*). To quote Gary Acton, a British oncologist;

"CART seems to me to be the most definitive personalized medicine we have achieved so far, in that each patient basically has a specific drug manufactured just for them".

Unfortunately, intensive care is usually required, and there have been some severe and fatal side effects in a few patients, which together with the huge cost ($400-500,000 per administration) add to the complexity of the debate about the value of this science-fiction strategy. We must remember though that all innovation is expensive at first. Indeed, there is little difference between the current cost of CART therapy and the early attempts at heart transplantation or ventricular assist devices. Costs fall with greater use.

Economic Issues

Can we pay for precision/personalised medicine?

Healthcare expenditure consumes a significant proportion of the national cake in most developed countries. We have established that many treatments are ineffective for certain individuals and may cause unpleasant and expensive side effects in others. It is hypothesised that personalised medicine will not only help patients, but also lower healthcare costs through early detection of disease, prevention, accurate risk assessments and efficiencies in care delivery as we move away from 'trial and error' approaches[22]. As I have already described, a key step in the process is appropriate testing of the patient and the identification of bio-markers which reflect the progress of the disease. One challenge has been to find the right balance between benefit for the patient and clinical value of the biomarker-based diagnostics and economic value for all the organisations involved.

Potential savings come from reducing the number of patients that need to be treated by more accurate diagnosis, reducing potential harm; avoiding the use of drugs (often expensive drugs) in patients who would not respond to the treatment; avoiding predictable (by the diagnostic test) side-effects; improving compliance (positive feedback from other patients) and improving health outcomes, reducing the burden of illness.

On the other hand, the cost of false positive or negative test results must be considered; very good tests may result in population screening, increasing the prescription of drugs; the costs of the tests themselves may be significant, especially as they will need to be repeated if used as biomarkers for disease progression; the costs of supporting the complex IT and data management can be high and the cost of maintaining privacy and confidentiality may be high.

Whilst there is clear promise that personalised medicine might one day reduce costs, most payers (governments and insurance companies alike) have been relatively slow to invest in the biomarker field. Jakka and Rossbach suggest[22] that this has been due to; i) difficulty in identifying which diagnostic tests, assays, IT and operational systems will truly save costs; ii) individual test costs may be modest, but cumulatively overall costs may be high; iii) data security is expensive and high risk, not least reputationally; iv) regulatory standards remain in flux; and v) no mechanisms exist which allow payers to work out the cost savings from prognostic testing. As Professor Raj Chopra has said[****], diagnostics is not a money-spinner for industry. In fact, industry would rather have cheap diagnostics and expensive orphan[††††] drugs for the limited number of patients in each group. There is also uncertainty about the best methods to use in studying the economic issues involved[23].

We have been made well aware of the costs of drug development. A recent report by the Tufts Center for Drug Development[####] estimated the average pre-tax industry cost per new prescription drug approval (inclusive of failure and capital costs) is **$ 2.56 billion (£1.87 billion)[§§§§].** About 30% of that expenditure in is pre-human development of the compound. A significant proportion of cost comes also from the clinical trials that are

[****] Personal communication

[††††] Orphan drugs are those that are not developed by the pharmaceutical industry for economic reasons, but which respond to public health need. The indications for such a drug may also be considered as ' orphan ' since a substance may be used in the treatment of a frequent disease but may not have been developed for another, more rare indication. See www.orpha.net

[####] (http://csdd.tufts.edu/files/uploads/Tufts_CSDD_briefing_on_RD_cost_study_-_Nov_18,_2014..pdf)

[§§§§] It has been argued by some that Tufts is supported by Big Pharma to produce high estimates of cost. It is thus easier to justify high prices.

required for regulatory approval. Costs of development have risen more than 10-fold since the 1970s [I am not sure if this is inflation adjusted; if it is not, then it could be a 60-fold increase]. Out-of-pocket development costs are currently rising by 10% per year and approval rates are falling. Over a 12-year period the Tufts group recorded **only a 7.1% approval rate** amongst the 1442 compounds tested. 80% had been discontinued at some stage during development, and a further 12.6% were still in development. Drug development is very expensive. Derek Lowe has parodied this as a reverse of Moore's law which he termed EMOORE's law[24]; "the cost of developing a new drug doubles roughly every nine years".

Why then would any company want to risk such high development costs when, almost by definition, the market for an agent successful in precision medicine is likely to be small, since one is deliberately, by biometric and genetic testing, constraining the number of patients to be treated? Obviously, drug development decisions will be based in part on the expected return on research investment, which is determined largely by expected revenues versus development costs[25], and the length of time that cash flow continues. If the company will sell only smaller quantities of a drug, then they are likely to need to be offset by either higher prices or lower costs. Certainly, it may be possible to justify higher costs on the basis of greater efficacy from the better targeted therapy, but payers will be very reluctant to pay the increased costs, especially if the number of such drugs the payers have to buy increases as it surely will.

Rees has pointed out[26] that there may well be important costs associated with converting the supply chain of the large pharmaceutical business from small stable molecules to large biologically active ones. Manufacturing processes are far more variable and complex than the traditional model based on chemical synthesis. This has been termed a vein-to-vein supply chain by some and will be difficult both to manage and control but in these days of improved temperature-controlled logistics this should not be an unresolvable problem.

It will be necessary to reduce development costs, and according to Wilke et al[25] such cost reduction is foreseeable. Costs would reduce if biometric testing can identify the patients most likely to respond to a given treatment early enough to reduce the sizes of Phase 1 and 2 clinical trials and increase the probability of success in Phase 3 trials. This cost reduction can only be realised if there is agreement to the strategy from regulators, who remain committed to studies requiring large numbers of patients, including non-responders.

Manufacturers are likely to seek to maximise revenue by launching specific biomarker tests in association with the relevant drug[27]. It can be argued that the combination of test and agent is what produces 'value' in terms of health gain and cost-offset. Test and drug are synergistic. Further, as tests develop, patent duration may be extended by re-marketing a compound in combination with a particular biometric test. For more detailed discussion of potential economic incentives for manufactures to move into this market see Towse et al[27]. Governmental organisations making approval decisions (NICE for example) are faced with complex decisions as tests multiply and patient groups become smaller[23]. The tools they have to assess the combination of drug and test become more complex, and decisions are likely to remain controversial as we adapt to this new form of medical practice.

Ethical Issues

Privacy, identity, morality

We are just a few decades on from the description of the structure of DNA, less than 30 years from the development of the internet and only 14 years from the first sequencing of the human genome. The rate of research in genetics, computing and medicine has been astonishing. So fast indeed that progress is often made before we realise the ethical and social implications of what we are doing. The inter-relationships between genomic data, clinical data, privacy, confidentiality and consent are complex and evolving.

I discussed earlier in this essay some of the issues relating to data sharing in relation to **biobanks**, but these banks raise particular ethical issues in relation to informed consent[28]. People permitting samples from their own body to be stored usually do so for altruistic reasons based on the explanation given to them at the time of the original consent, when the use of the samples and data associated with them is relatively simple, say to help in the diagnosis and treatment of your own particular disease. But how should we deal with potential *secondary* uses of those samples? Must the donor be re-consented, no matter how logistically difficult that is? How do we deal

with requests and authorisation for destruction of samples? What information should be fed back to donors, how often and by whom? And the core question of whose samples are they; the donor, the researcher or some entity, perhaps commercial, to whom the samples or data are passed or sub-contracted?

Biobanks are growing and becoming international. How should we deal with different cultural and consent regulations in different countries? The increasing complexity of these structures has led many in the field to think that relevant decisions should be taken by **proxy** independent structures, rather like research ethics committees, acting in the best interests of the donors, but balancing those interests against the common good. Simple up-front consent certainly does not seem to cover all the risks, but perhaps we should remember the original altruism and see contributing to the biobank or dataset to be a donation, similar in concept to blood donation.

What should one do if samples in the biobank, analysed later with newer tests reveal something of potential importance about the donor, perhaps a predisposition to a type of cancer not previously envisaged? Do the holders have a moral obligation to find, communicate with and explain that risk to the donor, or is it better for the donor to give up the right to know at the time of donation? If a familial trait becomes identifiable in time, should that information be shared with the family of the donor, or is ignorance bliss? And what if the data are lost, leaked, hacked or shared with an unscrupulous commercial partner? Who has what rights? It is essential that safeguards for privacy and confidentiality are written in (and well written) from the start, and that data security is maximised. Failure to do so would threaten the trust which is required to make personalised medicine work.

The development of **genetic testing** via rapid next-generation sequencing for prevention and diagnosis raises many ethical questions, especially since it has become a profitable commercial activity offered to the public via advertising (e.g. Helix, and 23andMe amongst others) letting you know about your susceptibility to certain types of cancer, diabetes, obesity etc., but also about muscle performance and baldness. Just this month Forbes reported that Helix had raised $200 million to compete with 23andMe[*****]. In the same Forbes article, Eric Topol, a cardiologist from Scripps, said it was possible to spend $1900 on genetic information with little proven value. Understanding the test's analytic and clinical validity as well as the true clinical utility of the knowledge gained, is crucially important, yet is likely to be poorly understood by a lay audience. The statistical concepts of probability, risk and variance on which the validities and utilities rely are difficult for many of us to grasp.

As with biobanks, the process and completeness of consent for genetic testing is equally fraught with potential risk. But it is a little more complicated. One might think of the test as relating to your particular condition, say diabetes, and be seduced into giving samples by that relationship. However, genetic testing is likely to reveal much more general information, which challenges the principle of patient autonomy, namely that one has a right to decide what to be or not to be tested for. The consent is complicated and should not just be a terms and conditions equivalent. Patients may well be very vulnerable at the time of consenting and easy to manipulate by the unscrupulous into participating. A third party, with no associated research or commercial interests in the testing might well be the best person to obtain consent, despite cost and complexity.

Who Owns The Data?

Surely the data belong to the patient

This raises the question of who owns the data, not only in the database itself, but after it has been shared. As Cordeiro[28] points out, raw genetic information held by institutions should not only be protected from access by third parties [especially profit-orientated entities] without consent, but should also be accessible to the individual from whom the information was obtained. There is strong evidence of the potential for profit-taking to be exploited in this area of science. In the 1990's, a company called Myriad successfully sought patent protection for an array of inventions associated with analysing gene mutations including, most controversially, DNA sequences[29]. They obtained multiple patents related to the BRCA1 and BRCA2 genes (those associated with breast and ovarian cancer) and began to commercialise the test for which they charged $4000. There was huge

[*****] https://www.forbes.com/sites/matthewherper/2018/03/01/helix-competing-with-ancestry-and-23andme-raises-200-million-for-marketing-war/#702db268485e

opposition to this, and eventually the American Civil Liberties Union filed suit against them. Eventually the case reached the US Supreme Court, and I reproduce here a paragraph from Kesselheim's excellent review of the case[29] [the emphases are mine] ;

> *"While ethical and policy arguments were a major feature of the debate surrounding the case, the decision focused squarely on the definitions of two codes: the genetic code and the patent code.* ***All nine Justices on the Court agreed that the segments of DNA that make up human genes are not patentable subject matter*** *under section 101 of the Patent Act because they are products of nature. However, the Court held, molecules reverse-transcribed from messenger RNA to eliminate intron sequences, so-called complementary DNA, or cDNA, are patentable. The decisive sentence of Justice Thomas's ruling crisply stated, "****A naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but cDNA is patent eligible because it is not naturally occurring.****"*

In concluding remarks Kesselheim says;

> *"The Universal Declaration on the Human Genome and Human Rights declares the human genome to be "the heritage of humanity" and that* ***"the human genome in its natural state shall not give rise to financial gains."*** *The Supreme Court quietly came to a similar conclusion, though with attention to preserving the incentives important for biomedical innovation."*

The possibility of commercial companies writing a blank cheque to themselves has been limited by this decision, but the Court recognised that some commercial incentive was needed to keep them interested and the door is not completely closed. However, we must keep a very close eye on what is being patented to ensure that research which is potentially socially advantageous is not exploited for excessive profit, rendering it the exclusive property of the rich, or diverting resources from other important areas of social policy. This is a field which demands both ethical and regulatory oversight. Because databanks are increasingly international, that oversight should be as uniform as possible. Regulatory frameworks already vary from country to country, even within Europe, for example in relation to direct to consumer genetic testing[30], and Brexit and the rise of protectionism threaten that internationalism.

MALIGN USE OF THE DATA

What if the bad guys get hold of your data?

Optimists may appreciate the dream of Desmond Tutu who donated his own cells for a study on genetic diversity. He is quoted by Cordeiro[28] as saying;

> *"My dream is that by including all peoples in understanding and reading the genetic code we will realize that all of us belong in one bid global family – that we are all brothers and sister. Wow!"*

He is an amazing, inspirational and inherently optimistic man, with a real belief in the inner goodness of his fellow men. But history, sadly, demonstrates that some humans wish to create divisions between peoples, and even destroy those that they think different, inferior or simply irritating. Examples abound; Hitler and the Jews, Hutus and Tutsis, immigrants to the US and native Americans, Myanmar and the Rohingya people. Just imagine how a modern-day Hitler might behave, armed with the information tools of the state acquires an extensive database containing the genomic information of individuals. I do not believe that he, or those totalitarians like him, would not use such data; "*find me all the people with*….". President Erdogan in Turkey has recently released the genealogy of thousands of Turks††††, an action perhaps relevant to the controversy over the genocide of the Armenians in 1915. We **must** put data security, privacy and relevant anonymization at the top of our 'to do' lists, even as we accept the general erosion of privacy in our daily lives that comes with social media and nationwide surveillance.

Access and Equity

†††† http://www.independent.co.uk/voices/turkey-race-armenian-recep-tayyip-erdogan-generlogy-family-trees-ethnicity-a8234346.html

Who has access to these treatments?

Nicolas Rose of the London School of Economics raises perhaps the most telling ethical criticism. He argues[1] that *"The focus of all this activity is on the diseases of affluence and not on the conditions that ail most people on our planet, curtailing their life expectancy and bringing them to an early death"*. He is right; most of the world won't have access to genomics or patented medicines. He goes on to argue that even judged by its own standards, the field raises issues which should cause us to pause and think. He asks, are we happy to 'rush headlong' into a future of medicine based on prediction and prevention? What are the implications of being determined to be 'at risk', for yourself, your family, your employers, your insurers and so on? Will you be stigmatised, become depressed or isolated? He points out that early intervention on asymptomatic individuals based on tests may prove later to be unreliable, over-predicting and leading to a huge market for risk-reducing drugs (as we have seen with statins); almost everyone becomes a suitable case for treatment.

Access to personalised medicine is limited in much of the world. These issues have been highlighted in a very moving article[31] from Bosnia (http://ascopubs.org/doi/full/10.1200/JGO.2016.008698). This paper describes the frustration of knowing that new and effective treatments available, having the patients who would benefit from them, but having neither the biological tests or drugs to deliver those treatments. They describe a clear mismatch between scientific knowledge and political knowledge and will. The current prices of these therapies are set in markets which are affluent and privileged.

A common theme running through much of the criticism is the distrust of what has become known as Big Pharma. There is not space to explain how that distrust has developed, nor to explore further predictions of all the ways in which the technology surrounding personalised medicine might be commercially exploited. However, because of the sensitivity of the data involved, because of the potential social implications of identifying sub-sections of the population and because of the huge potential costs involved, trust must be a key element in development. Trust needs to be fostered by all involved, openness and transparency are crucial, and every aspect must be ethically reviewed and properly regulated. People and companies WILL profit from it, and some will do so with excessive vigour.

Developing Issues

The more you discover, the more you extend the need for discovery

The complexity of the research in precision medicine should not be underestimated. In common with much of medicine, the more you discover, the more you extend the need for discovery. Just this week, workers in Quebec have highlighted[32] the impact of the environment on the human genome, adding more data requirements to the mix. Their paper revealed *"a substantial impact of the environment on the transcriptome‡‡‡‡‡ and clinical endophenotypes§§§§§, **overpowering that of genetic ancestry**. Air pollution impacts gene expression and pathways affecting cardio-metabolic and respiratory traits, when controlling for genetic ancestry. Finally, we capture four expression quantitative trait loci that interact with the environment (air pollution). Our findings demonstrate how the local environment directly affects disease risk phenotypes and that genetic variation, including less common variants, can modulate individual's response to environmental challenges"*. It is not just the genes, but the environment too which influences the course of disease.

Concluding Remarks

I am inherently optimistic, and I take the view that much good will come from the research and progress associated with personalised medicine. Its scope is infinite, and the idea that treatment will be better focussed, less wasteful and associated with reduced harm is clearly most attractive. Cancer therapy is already being revolutionised by the development of biomarkers and genetic testing, and drugs are now much more specific (and often less toxic) than ever before. We should be grateful for this and look forward to greater and even more rapid progress as orphan drugs and rare diseases become the focus of corporate and research attention.

‡‡‡‡ The sum total of all the messenger RNA molecules expressed from the genes of an organism.
§§§§§ Endophenotype is an epidemiological term used to connect behavioural symptoms with more well-understood structural **phenotypes** associated with known genetic causes or with abnormal genetic testing.

But as I hope I make clear, it is not a field without risks of profiteering, exclusivity and loss of privacy. It now has a momentum of its own, and is being supported enthusiastically by Universities, grant giving bodies and of course by business, all of whom now wish to share any benefit by divvying up the Intellectual Property and discovery rights. It is not going to go away.

The concentration of work is largely on cancer and rare diseases as the genetics are further advanced in those areas and there is a big market in affluent countries. But Rose is right; millions of people in Third World countries do not have access to the health care, drugs and vaccines which are available in developed countries. Ten million children less than 5 years old die each year of infectious diseases for which treatments exist in developing countries. 3 million children die each year because they have not been immunised. 150 million women would like to wait longer between two pregnancies or limit them, but they do not have access to contraception. Epidemics, war and water shortage only widen the health gap between poor countries and developed countries. These are political and economic problems, and not primarily medical.

Should this inequity inhibit research into personalised medicine? I don't think so; most of the treatments we have developed in the modern era of medicine have started in the affluent parts of the world, and this is likely to continue because of the infrastructure and incentives. The Gates foundation would argue that the genomics revolution is **more** likely to impact on disease of the poorer and emerging world, e.g. genetic testing for thalassaemia, new targets for TB, malaria and trypanosomiasis.

The science around personalised medicine is already demonstrating the benefits of close cooperation between disciplines (genetics, computing, clinical medicine, data scientists) and cultures (private and public sector, academic and clinical). It is true that the progressive segmentation of the market into smaller and smaller groups of patients creates difficulties for manufacturer and purchaser alike. But successful research will mean more effective treatments and hopefully lower costs (perhaps by exploiting orphan drugs[******]), particularly if complications and wasted treatments are minimised.

It is clearly morally right that we aim to get the right treatment to the right patients at the right time, and it may be that costs need to be shared in a more creative way, in the manner say of subsidising bus services which are not commercially viable, but socially necessary. We must look to industry to identify cheaper and more rapid ways of developing agents for this growing demand, and we must look for a regulatory system more relevant to the smaller, more specific populations identified by genetic testing.

Provided that we can maintain the ethical and regulatory control required of a civilised society, and minimise the cost of implementation, it seems to me likely that in time we will all benefit from precision, personalised medicine.

With Special Thanks

[******] Orphan drugs are those that are not developed by the pharmaceutical industry for economic reasons, but which respond to public health need. The indications for such a drug may also be considered as 'orphan' since a substance may be used in the treatment of a frequent disease but may not have been developed for another, more rare indication. See www.orpha.net.

This is a tough topic for a surgeon. It didn't exist when I graduated, and much of the basic science now taught at medical school passed me by. I could not have written this without the help of these great colleagues and advisors:

Gary Acton (UK)
Charles Alexander (London)
Professor Adam Cohen (Leiden, The Netherlands)
Professor Carl Backer (Chicago, USA)
Professor Martin Birchall (London)
Professor Geoffrey Bird (Philadelphia, USA)
Professor Raj Chopra (London)
Professor Meryl Cohen (Philadelphia, USA)
Abigail Cooper (London)
Professor Jo Delahunty QC (London)
Lesley Elliott (London)
Jake Arnold Foster (London)
Professor Richard Jonas (Washington DC, USA)
Vanya Loroch (Switzerland)
David Matthew (London)
Parker Moss (London)
Professor Jim Quintissenza (Lexington, USA)
Hedley Rees (London)
Professor Bob Sade (Charleston, USA)
Professor James Tweddell (Cincinnati, USA)
Professor Bill Williams (Toronto)
Professor David Winlaw (Sidney, Australia)
Giovanna Zacchettti (Italy)

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