



postnote

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PERSONALISED MEDICINE

Risk of disease and response to treatment varies from person to person. This is due to variation in human genetic coding, interactions between one's genes and environment over a lifetime and the unique signature of the immune system. Defining the scope and nature of human biological variation allows the targeting of medical treatments to those most likely to benefit. Such treatments may include drugs or cell therapies tailored to a patient's history, genes and immunology. This POSTnote examines the state of research into human variability, and the prospects, challenges and policy implications of more personalised medical treatment.

Personalising Medicine

Good clinicians have always tailored treatments to alleviate symptoms and reduce side effects, but generally this relied upon trial and error. Personalised medicine may improve upon 'reactive' medical diagnosis by predicting treatment response or preventing disease before symptoms appear.

Personalised medicine holds both promise and cause for concern. Selective treatment may limit access to those most likely to benefit, whereas following a 'one size fits all' approach to medical research and development may have benefited the widest number of potential patients. Nevertheless, explaining the environmental, genetic and other biological sources of human variation will alter the way diseases are diagnosed, drugs are developed, and the matching of therapeutic cells and tissues to patients.

Classifying Human Biological Variation

Historical attempts to classify human variation often assigned individuals to racial categories. While ethnic identity has a complex relationship to health, tailoring medical treatment to assumed biological differences based on race is problematic and imprecise (see POSTnote 276). The measurement and understanding of the influences of genetic, environmental and immune factors on human variation is improving. If classifying patients according to these factors predicts susceptibility to disease or clinical response, medical treatments can be more precisely targeted.

Developmental and Environmental Variation

Many biological characteristics are neither exclusively genetic nor environmental. Childhood development, diet, exposure to toxins and microbes, and socioeconomic status all profoundly influence health. This information is especially important in understanding patterns of growth and susceptibility to disease. Gene-environment interactions are complex and the relative contributions of multiple factors are difficult to quantify. However, personal patient histories are crucial to tailoring medical therapies. Without knowledge of environmental factors, genetic tests for common diseases hold little value.

Human Genetic Variation

Genetic variation ranges from single changes at one point in the DNA, to widespread switching around, repeating, or deletion of parts of the genome with potential consequences for the regulation of a large number of genes or biological processes (Box 1).

Box 1. DNA, Genomes and Variation.

DNA is the chemical code of instructions that direct the building and actions of cells, and thus biological processes. These instructions are spelt out in strands of bases. Sequencing reads these bases; a genome is the entire DNA sequence of an individual. About 2% of the human genome is made up of genes, the functional units of DNA that code for proteins. The rest of the genome is called 'non-coding', but may regulate gene function specifying where, when, and in what quantity proteins are made.

Humans vary in their inherited DNA sequences in a range of ways, from variations in single bases (single nucleotide polymorphisms or SNPs) to insertion or deletion of several bases or thousands of bases, to the duplication of DNA segments more than 1,000,000 bases long. The majority of known genetic variations in humans are SNPs, with over 10 million known locations where an individual may vary by a single letter in their DNA.

At present, most known human variations are at single points, as only a handful of complete human genomes have been sequenced. But the years following the first complete human genome sequence have seen a decline

in both the cost (from millions to tens of thousands of pounds) and time (from years to months) required to decode a person's entire DNA sequence. As the number of complete sequences increases, comparative studies will reveal more fully the extent to which human genomes vary and the importance of variations.

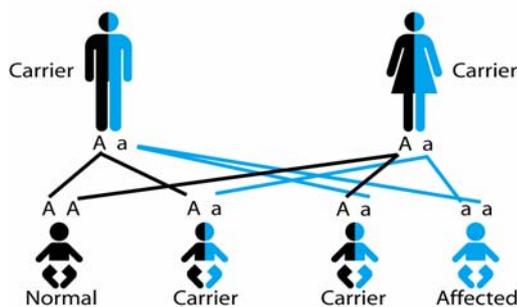
Current understanding of human variability indicates:

- The relatively small overall genetic variation suggests a high degree of relatedness within our species.
- Known regional and ethnic variations do exist, however, and can be quite dramatic. For instance, distinctive adaptations to dietary differences (e.g. the ability to digest milk sugar), and disease susceptibility (e.g. resistance to malaria) appear at high frequencies where they are regionally important in human history.

Measuring Genetic Variation

Links between genes and disease fall into two broad categories: those where risk is linked to one gene with a predictable inheritance; and those where it is due to multiple genes interacting with the environment.

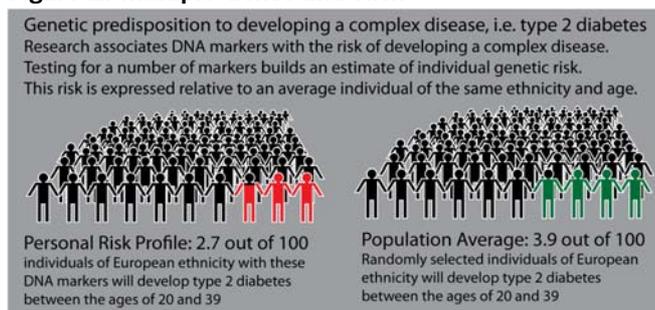
Figure 1. Inheritance of Single Gene Disorders



Single gene disorders

More than 2,000 diseases have been linked to mutations of a single gene. These include cystic fibrosis and Tay-Sachs disease which are rare, linked in a very predictable way along family lines (Figure 1), and often have severe consequences. For example, people inheriting two copies of a mutated gene (one from each parent) suffer from the disease, while those with one copy (carriers, see Figure 1) do not. Preventative treatment is limited unless it targets a physiological mechanism affected by the gene.

Figure 2. Multiple Genes and Risk



Multiple genes associated with common disorders

Most common disorders like type II diabetes or hypertension are not traceable to the action of a single gene. They are complex, involving multiple genes interacting with one another and/or environmental

factors. The associated genes have minimal individual effects, are numerous, and two individuals with the same condition rarely have the same combination of these genes. Genetic predisposition to developing complex disorders is often expressed as a risk profile (Figure 2) which compares an individual's genetic likelihood of developing a disorder relative to the average population.

Non-inherited or Non-genetic Characteristics

Beyond inherited DNA, variation extends to cancerous cells of tumours or how DNA is packaged and read.

Mutations/DNA damage

Some cancers are caused by uncorrected damage (mutations) to DNA that accumulate over a lifespan. Such tumour cells have a different genotype from other cells in the body. Testing tumour DNA may allow clinicians to target it with the correct treatment (Box 2).

Box 2. Targeting Tumours

Herceptin screening: While many breast cancer patients display similar clinical symptoms, only a subset of patients may benefit from the drug Herceptin. This is because Herceptin targets a type of protein found on the tumours of roughly 1 in 4 breast cancers. The label advises testing for the protein before administering Herceptin as a method of targeting treatment to patients most likely to benefit.¹

Tailoring immunity: The DNA of cancer cells codes for tumour-specific proteins not found in the DNA of healthy cells. A patient's immune system potentially can detect these tumour proteins and eliminate cancer cells, but this does not appear to happen in sufferers of cancer. If clinicians were to identify these proteins and design a 'tailored' vaccine, it is hoped this would alert immune recognition and induce an effective anti-tumour immunity.

Epigenetics

Variations in the way genetic material is packaged and read influence gene activity without altering the sequence of DNA. These (epigenetic) factors may switch genes on or off in response to environmental cues such as diet, and some appear to pass on from parents to offspring.

Patterns of these 'imprinted' modifications in identical twins are different despite their having the same DNA, and these differences accumulate throughout life. Epigenetics may help explain cases where just one twin develops a complex disease. It may also explain individual variation in drug responses or currently unknown causes of cancers. Potentially, therapies tailored to epigenetic characteristics would be more easily reversible and less complex than directly altering a patient's DNA (a process called gene therapy, see POSTnote 240).

Diagnostic Testing

The success of any type of personalised medicine will be critically dependent on accurate diagnosis. Indeed, the specificity and reliability of diagnostic tests limits the degree to which a treatment can be personalised. This section looks at the main types of diagnostic tests that are under development and the issues that these raise.

Biomarkers

Clinicians generally use physical symptoms to identify an illness. However, two patients with identical symptoms might be suffering from very different conditions. This is important if the genes or biological pathways involved require different treatments. Diagnostic tests of selected biomarkers (Box 3) discern which genes or processes are influencing a patient's health and response to treatment.

Box 3. Biomarkers as Measures of Variation

Biomarkers are measurable material indicators of current health status, or predictors of susceptibility to disease and likely effectiveness of treatment. Genetic information is one of many such indicators. Other biomarkers include the products of genes or metabolic activity, such as proteins, hormones, RNA or other signalling molecules used by cells. Biomarkers are used in clinical practice to:

- predict or identify risk of disease;
- diagnose and assess severity of existing disease;
- stratify patients to potentially tailor treatment.

Genetic Diagnostic Testing

At present, most clinical genetic tests look at a selection of points on the DNA where there are known associations with a single-gene disease or response to a drug. For example the genes BRCA1 & BRCA2 are associated with a high risk of breast cancer. Patients with family histories of breast cancer can be tested for these genes and flagged up for regular screening. Likewise, a test for carriers of untreatable inherited conditions may influence a couple's reproductive decision making.

Whole genome sequencing is still too expensive for widespread application in patients, but sequencing technology is anticipated to reach a benchmark "\$1000 genome" soon. Then, the routine collection of an entire patient sequence becomes economically feasible. But technological innovation may outstrip the translation to clinical applications. Thus, the Human Genetics Commission has suggested that, "...the ability to sequence the genome has the potential to obscure the challenges that exist in understanding the data being generated...and deciding whether and how it should be introduced into clinical practice."²

Risk profiling

With complex common disorders, there are currently limited conclusions that can be drawn from a genetic test. The results of such tests depend upon the number of DNA markers tested and the strength of the published research linking them to a particular condition.

Critics of predictive testing for complex disease point to the lack of proven medical benefit. Psychosocial research has found little evidence of genetic test results prompting sustained healthy or preventative behaviour from patients at high risk of a complex disease. Conversely, there is also little evidence that such test results bring long-term negative psychological impact. Supporters of free access to personal genetic data, including private test providers (see below), caution against excessive regulation impeding the desire to know details of one's own health.

Personal Genomics Companies

Private companies now offer direct-to-consumer genetic tests, ranging from reading a selection of points on the DNA to complete genome sequencing. They claim to provide information on a customer's ancestry or 'recreational' non-medical genetic information as well as risk of developing single gene and complex diseases.

Regulation of Genetic Tests

At present, tests are regulated in the UK as devices under the European In Vitro Diagnostic Device Directive (IVDD), enforced by the UK Medicines and Healthcare Products Regulatory Agency (MHRA). These regulate test methods and equipment, but not whether conclusions or medical advice drawn from the results benefit the consumer. This has been a source of concern, as private companies analysing the same person's DNA may draw different profiles of disease risk. The Human Genetics Commission is currently establishing a framework of principles for direct-to-consumer testing.

Personalised Medicine in Practice

One approach to the use of detailed knowledge of human variation to tailor medical treatments to patients (the subject of an upcoming POSTnote on regenerative medicine), is to develop personalised cell therapies to match therapeutic cells to the patient's immunology (Box 4). The other main approach is tailoring drug treatments to take account of genetic variations (pharmacogenomics) and this is discussed in more detail below (and the subject of an upcoming House of Lords Select Committee on Science and Technology report on Genomic Medicine).

Box 4 Personalised Cell Therapies

Stem cell therapies

Stem cells can be used to replace damaged or diseased tissue (see POSTnote 174). Approaches to minimising immune rejection include:

- Using donor stem cell banks to match a donor cell line to the patient, based on immunological categories. This is similar to the 'personalised' matching of blood groups for transfusions or tissue type for organ transplants.
- Creating a customised line of immunologically acceptable cells from adult stem cells isolated from the patient. Tissues such as cartilage and skin can be grown from a patient's own cells and future technology may extend personal cell preparations to other cell types, or larger or more complex cells and organs.
- Creating matched cells that behave as embryonic cells - a possible future approach. This may be done through transfer of DNA to an embryonic cell or by inducing the patient's adult cells to 'reset' to an embryonic-like state. Such cell lines potentially could be used to derive a very wide range of cell types and tissues, and could also get around issues such as tissue rejection and disease. However, personal stem cell lines may prove costly and time-consuming and raise controversial ethical issues.

Pharmacogenomics

Humans vary in their responses to drugs. Genetic factors may account for 20-95% of this variation³, so diagnostic tests might predict individual variation in response to medication (see Box 5). Current pharmacogenomic research mainly involves the prediction of appropriate

dosage or avoidance of negative responses to a drug. Discoveries are based on associating observed drug responses with specific genetic markers. This research may eventually lead to designing drugs to interact with specific genes, or targeted to specific metabolic processes 'flagged up' by similarities between patient genomes.

Box 5. Pharmacogenetics/Pharmacogenomics

Pharmacogenetics is the older term referring to inherited differences in the ways patients process drugs, while pharmacogenomics generally also encompasses potential development of novel drugs based on genomic information.

Genes code for the cell surfaces, processes and organs targeted by drugs as well as the enzymes that metabolise them. These affect the speed at which a patient processes a drug and the degree of his or her response. If diagnostic tests can identify these genes, patients can be stratified into genetic subgroups. This allows doctors to administer drug treatment only to individuals able process the drug in the desired way, and to tailor the treatment dosage to maximise efficacy and to reduce toxicity and adverse drug responses.

Regulating pharmacogenomics

Diagnostic testing to predict safety and efficacy is increasingly common. There are separate regulatory regimes for drugs and the diagnostic tests used to target them. Drugs are assessed by the MHRA or the European Medicines Agency (EMA), diagnostic tests are regulated under the IVDD. Approval of a drug is not necessarily conditional on using it with a particular type of test. If a drug is referred to the National Institute for Health and Clinical Excellence for appraisal, then it may consider the whole 'package' (drug plus test) as in the case of Herceptin (see Box 2). However, healthcare providers vary in how closely they adhere to such guidelines.⁴

Medical education and training

At present, the application of pharmacogenomic diagnostic tests is limited to a relatively small number of treatments. The most immediate applications of pharmacogenomics are in the field of cancer treatment where drugs are already targeted to small groups of patients, and the level of clinical specialisation is high. However, as personalised medicine moves into other specialities and primary care, clinicians may need training for new personalised therapies via continuing professional development. At present, use of a recommended genetic test prior to prescribing a drug can vary widely across disciplines.

Health economics

Personalised medicine will reshape pharmaceutical research and development and the calculation of cost-effectiveness by health services. The previous business model was based on so-called blockbuster drugs, intended for general use in the population and generating annual global profits in excess of \$1 billion. Profits from blockbuster drugs offset the expenses of regulatory approval and investment in research and development.

As drugs become more specialised to genetic subgroups, the economic model will have to address incentives for developing drugs with small markets. Proponents of

personalised medicine suggest drugs abandoned in the development stage for lack of effect or unacceptable side effects in the general population might be 'rescued' by selective trials and approval for genetic subgroups. Such selective clinical trials and conditional approval might also reduce the time and expense of the drug regulatory process. But no prediction or test is 100% effective and such conditional approvals might exclude patients who might benefit or fail to exclude all who may be harmed.

Research projects to link genes with risk of complex disease require large investment and collecting genetic and health information on thousands to hundreds of thousands of individuals. Critics of research into genetic determinants of health suggest that behaviour modification would prevent more illness than linking specific genes to the causes of disease. For instance, an Oxford Health Alliance initiative⁵ lists three behaviours: poor diet, smoking and lack of exercise as major contributors to four diseases that cause 50% of the world's deaths. Behavioural change may have greater impact on the overall health of the population than personalising therapies for individual patients.

Overview

- Human variation results from interactions between genes and the environment and can shape a person's response to drugs and chances of developing disease.
- Personalised medicine tailors treatment to patient subgroups based on their biological characteristics.
- Most human genetic variation is categorised according to known points in DNA where individuals vary by a single code. Sometimes this explains the cause of a disease or how well a drug works, but more often a number of variations subtly influence overall risk of disease or response to treatments.
- As understanding of biological factors regulating gene activity improves and whole genome sequencing becomes less costly or time consuming, future personalisation of medicine will include other measures of variation and specialisation of treatment.
- Economic incentives, regulation of biological tests and medical education will influence the rate and degree to which personalised medicine will be incorporated into drug development and clinical practice.

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Endnotes

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