We all strive to define ourselves as an individual, distinguished from the crowd and defined by our own desires and experiences. We are exactly this: biologically unique, and (with the exception of identical twins) the owners of a distinct pattern of DNA unlike anyone else’s. It therefore seems antiquated, in a world more accepting of difference than ever before, to accept a universal, generalised idea of how a person will respond to a drug.

***Creating an Individual***

The human genome is the instruction manual for building a person. DNA, the language of the text, is comprised of sequences of nucleotide bases which are split into sections known as genes. Each gene is responsible for encoding the information to create a specific protein.

The genome remains largely similar from person to person with small variations or glitches (in lay language) known as polymorphisms present in everyone. These are either germ-line (inherited) or somatic (acquired).

An allele is a variant form of a gene caused by a polymorphism. If a specific allele occurs in less than 1% of a population, it is typically termed a mutation. Whilst many polymorphisms do not significantly alter gene function, some affect gene expression or the structure and ultimately the activity of the encoded protein. These are of particular interest with regard to diagnostics and therapeutics.

These instructions are also influenced by “epigenetic” modifications which can influence gene expression via mechanisms such as switching off an activated gene. These modifications can be due to factors such as age, lifestyle or disease and can result in potential alterations to the expression of phenotypes without changing the underlying genotypeXXXii.

Pharmacogenomics investigates genetic variation in drug response. The aim of pharmacogenomics is to improve the safety and effectiveness of drug treatment by using genetic information to inform prescription decision making, much like we currently take renal function into account when prescribing drugs that are eliminated by the kidneys. To do this, genetic variants that influence drug response are first identified, characterised and then used to stratify patients into subgroups that receive subgroup-specific genotype-informed prescriptions. Therefore, pharmacogenomics is a cornerstone in the ongoing endeavour for precision medicine, also known as stratified or personalised medicine.

The term “pharmacogenetics” is by no means a neologism and was first coined by the German geneticist Friedrich Vogel in 1959[[1]](#endnote-1). However, the concept that innate factors can affect drug response dates back as far as Pythagoras[[2]](#endnote-2). Pharmacogenomics is often used interchangeably with pharmacogenetics, and was first used in 1997.

Currently a “trial and error” approach remains the mainstay of prescribing, with some degree of individual tailoring based on factors such as age, weight, biochemical markers and co-morbidities. We know, however, that despite these considerations some patients do not respond in the expected manner. The number of patients who respond beneficially to a given drug can be anything from 25-80%[[3]](#endnote-3). Furthermore, in the region of 6% of hospital admissions are related to an adverse drug reaction (ADR)[[4]](#endnote-4), and drug tolerability issues are associated with poor medication adherence[[5]](#endnote-5). Pharmacogenomics aims to offer clinical decision support to improve the benefitrisk profile of prescribed medications.

**The Genetics of Drug Response**

It is estimated that over 97% of people carry at least one variant in a gene that can influence drug response through perturbing either the pharmacokinetics or the pharmacodynamics of a drug[[6]](#endnote-6). For example, some genetic variants impact on drug pharmacokinetics by affecting genes involved in drug ADME: absorption, distribution, metabolism and excretion, including drug-metabolising enzymes (e.g. cytochrome P450 isoforms, CYPs) and drug transporters. Genetic variants can also influence both a drug’s on-target and off-target pharmacodynamic effects.

The majority (over 80%) of ADRs which lead to hospital admission are type A reactions[[7]](#endnote-7), which are predictable from knowledge of a drug’s pharmacology and usually result from excessive drug activity through increased systemic exposure and/or increased sensitivity of the target site to the drug.

The identification of mutations is also being used to design new drugs which must be used in patients with that mutation. This is relevant for cancer medicine, where pharmacogenomics will have increasing relevance. For example, vemurafenib was designed to inhibit the V600E mutation in the BRAF gene in metastatic malignant melanoma[[8]](#endnote-8). The use of targeted therapies, such as trastuzumab[[9]](#endnote-9), in HER-2 positive breast cancer is another example. Similar approaches are now also being used for the germline genome. For instance, ivacaftor is a novel therapeutic licensed for patients with cystic fibrosis (CF) carrying certain pathogenic mutations in the CF faulty protein, CFTR. This is because ivacaftor binds to and partially restores the activity of CFTR. However, it only works in patients carrying specific *CFTR* mutations, and thus requires a knowledge of the genotype before prescribing.

**P450 genes:** The effect of environmental influences on *CYP* metabolising activity and drug response is extensively covered in the pharmacy curriculum (e.g. drug-drug and drug-food interactions). However, a large number of *CYP* genes are polymorphic, and therefore, the influence of genetics on variation in response should not be underestimated.

“Metaboliser phenotype” is the term used when predicting the activity of a drug-metabolising enzyme in an individual patient, based on the gene alleles the patient carries and prior knowledge of the typical activity level of each allele. This can for some enzymes, for example, *CYP2D6*, lead to 4 different activity phenotypes: “poor metaboliser”, “intermediate metabolizer”, “extensive (normal) metabolizer” and “ultra-rapid metaboliser”.

There are over 100 different *CYP2D6* allelic variants presently recorded[[10]](#endnote-10);and around 6-10% of Caucasians are considered poor metabolizers; however, the incidence varies amongst ethnic groups with less than 1% of Asians and 2-5% of African-Americans lacking the enzyme[[11]](#endnote-11). CYP2D6 is responsible for the metabolism and/or activation of around 25% of prescribed drugs[[12]](#endnote-12) including, for example, codeine. Codeine is a prodrug and a small proportion (~0-15%) undergoes O-demethylation to morphine in the liver via *CYP2D6*[[13]](#endnote-13). However, due to the polymorphic nature of *CYP2D6*, the combination of alleles present can determine the extent to which this occurs. Importantly, the *CYP2D6* ultra-rapid metaboliser phenotype (where there are more than two copies of the gene) has been associated with fatal cases of opiate toxicity in patients administered codeine, due to increased codeine biotransformation to morphine. This prompted the EMA to review codeine use and led to the current MHRA restrictions[[14]](#endnote-14). Around 2% of Caucasians are ultra-rapid metabolisers while 29% of Ethiopians carry more than 2 copies of the gene.

Identification of poor metabolisers is also important to circumvent issues such as clopidogrel resistance. Like codeine, clopidogrel is a prodrug that requires biotransformation into the active thiol group-containing moiety that inhibits ADP-induced platelet activation. The degree of platelet inhibition amongst individuals taking clopidogrel is highly variable[[15]](#endnote-15) and this potentially results in life-threatening sequelae such as stent thrombosis. *CYP2C19* is one of the principal enzymes involved in clopidogrel activation. In contract to CYP2D6, around 3-5% of Caucasians are deemed poor metabolisers, rising to 12% to 23% of the Asian population[[16]](#endnote-16).. The FDA issued a black box warning in 2010 advising about the association[[17]](#endnote-17).

**Transporter genes:** In addition to determining enzyme function, polymorphisms also affect drug transporter proteins, structures responsible for the movement of ions and molecules across biological membranes . A notable example is SLCO1B1, a gene encoding a protein known as OATP1B1, which is responsible for the intrahepatic transport of multiple compounds, including statins. Some *SLCO1B1* variants have been associated with lower uptake of statins (in particular, simvastatin), increased drug exposure, and a higher risk of simvastatin intolerance and myopathy[[18]](#endnote-18).

**HLA genes:** Pharmacogenomics facilitates insight into the underlying mechanisms of ADRs and can predict susceptibility to some idiosyncratic (type B) ADRs. An important class of genes are the human leukocyte antigens (*HLA*); specific *HLA* alleles can increase susceptibility to immune-mediated idiosyncratic ADRs through off-target mechanisms. An example is the effect of *HLA-B\*57:01* on abacavir hypersensitivity[[19]](#endnote-19). The SmPC for abacavir mandates *HLA-B\*57:01* typing prior to the use of abacavir. This is also mentioned in guidelines from organisations such as the British HIV Association[[20]](#endnote-20), advising pre-emptive *HLA* genotyping to identify high risk individuals. Another example is the association of *HLA-B\*15:02* with carbamazepine-induced toxic epidermal necrolysis[[21]](#endnote-21); this HLA allele is particularly prevalent in SE Asian countries.

In short, therefore, improving patient outcomes is just one of the potential benefits of pharmacogenomics. In an environment of increasing demand and limited resources, the projected annual costs to the NHS of medication-related hospital admissions is around £466 million[[22]](#endnote-22) with a further £300 million spent on unused medications[[23]](#endnote-23). A personalised prescribing approach strives to reduce ADRs and ineffective prescriptions to provide a smarter, more cost-effective way to manage the medicines budget. However, implementation of such innovative approaches has many challenges.

**Barriers to Implementation**

The past decades have seen multiple advances within the field of genomics; not least the completion of the Human Genome Project in 2003. This milestone and the contemporaneous statement of requirement for a ‘genetically literate’ primary care workforce by the Human Genetics Commission[[24]](#endnote-24) set high expectations for a paradigm shift towards genomics becoming routine in clinical care, spearheaded by pharmacogenomics. However, nearly 14 years later, even the integration of pharmacogenomics into standard clinical practice overall has been limited.

Multiple factors have been cited as reasons for this slow transition. First, there is a lack of understanding of the topic and its application amongst healthcare professionals. It is a relatively novel discipline, and the knowledge base therefore remains incomplete. Second, a lack of evidence-based implementation guidelines is a large hindrance for the field’s appropriation into general clinical practice. Third, ethical issues surrounding genetic information may be of concern to some patients and healthcare professionals. Fourth, the lack of clear guidance on the requirements and consequences of testing continue to deter some[[25]](#endnote-25).

Another major obstacle to implementation is the availability and expense of testing. However, the cost is decreasing all the time. While the first human genome cost in excess of $3 billion, the cost now is <$1000 with the advent of next-generation sequencing technologies. However, equipment, trained personnel and strict quality control procedures are still required, and seldom available outside specialist units.

Finally, deficits in prescriber knowledge surrounding translating genetic information into clinical action points[[26]](#endnote-26) may also contribute to the poor uptake of testing. On-going efforts to collate evidence and information for clinical utilisation have been fruitful and the Pharmacogenomics Knowledgebase (PharmGKB.org) provides a repository of pharmacogenomic-based drug dosing clinical guidelines from multiple sources including the Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG)[[27]](#endnote-27) .

Despite these barriers there are some genomic tests within the UK which have become fundamental to routine care. A notable example is that of thiopurine S-methyltransferase (TMPT) polymorphisms which can account for around 10% of overall thiopurine toxicity[[28]](#endnote-28). As a result, the British National Formulary now recommends phenotype or genotype screening as standard prior to initiation.

**Moving into the Future**

Despite the challenges, the future remains optimistic for pharmacogenomics. The Translational Pharmacogenetics Program is an implementation initiative instigated by the US Pharmacogenomics Research Network (PGRN) and aims to overcome the barriers that currently limit pharmacogenomic testing in clinical practice[[29]](#endnote-29).

Simultaneously, within Europe, the Ubiquitous Pharmacogenomics Consortium (U-PGx) is commencing the first large, international implementation project to determine the impact of pre-emptive testing on ADR frequency, severity and associated costs[[30]](#endnote-30).

Industry and regulatory bodies have, themselves, begun to adapt, spurred by opportunities to re-trial previously abandoned compounds (e.g. bucindolol) or reduce ADRs in marketed products. As a result, incorporating genomic data into drug design and safety information is becoming common practice. Analysis of 517 EMA summaries of product characteristics documented that nearly 15% contained utilisable pharmacogenomic information[[31]](#endnote-31).

This shift into precision medicine is changing the business model of the pharmaceutical industry, moving away from the generic “block-buster” style of drug development into, potentially more expensive, receptor or biomarker targeted therapies such as imatinib or ivacaftor.

This transition has forced the industry to view its role beyond solely the manufacture of the therapeutic and into the realms of companion diagnostics. These kits and assays allow precision medicine to be truly effective by identifying, as accurately as possible, the patients underlying disease mechanism or predictive biomarkers. Such technologies are already being used in clinical practice, with regulatory agencies approving cetuximab to be used as part of the first line regime for KRAS Mutation-Negative (Wild-Type) Epidermal Growth Factor Receptor (EGFR)-Expressing Metastatic Colorectal Cancer as well as approving the first KRAS companion diagnostic test kit, the QIAGEN *Therascreen[[32]](#endnote-32).*

It is important to recognise, however, that whilst the germline genome remains constant over a lifetime, gene expression levels may change. The realisation of personalised medicine will require holistic assessment of the patient which will include not only genomics, but also environmental factors, disease status and age-related changes.

In the UK, the NHS outlined its plans for integration of personalised medicine in 2016, aiming for whole genome sequencing to be standard for specific conditions by 2020. The advent of the 100,000 Genomes Project and the sale from retail pharmacies of the home genetics kit, *23 and me®*,are further indicators of the need for pharmacists, in all areas of the profession, to become familiar with the principles of pharmacogenomics and its evolving application into clinical practice.

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