Pharmacogenomics – A Tailor-made Medicine

Recently, health care has been shifting from a “one size fits all” model to a precise personalized regimen. Modern medicine urges the clinical implementation of “the right drug, right dose, right time, and right way” approach of treatment in the medical field. Although the tailoring of treatment dates back to the time of Hippocrates, the term has risen in usage in recent years given the growth of new diagnostic and informatics approaches that provide understanding of the molecular basis of disease, particularly genomics. Pharmacogenomics (PGx) is the driving force behind this new therapeutic approach, and it involves the use of genetic information to improve the clinical outcomes of pharmacotherapy.

What is Pharmacogenomics?
Pharmacogenomics (PGx; pharmacology + genomics) is an integral part of personalized medicine (PM) which is the study of how genotype affects drug response and aims to:
1. improve drug development
2. reduce adverse reactions
3. maximize efficacy in drug dosage and prescription

PGx is momentous for PM, because different patients respond differently to a similar drug. It analyzes how the genetic makeup of an individual affects his/her response to drugs and recognizes genetic variants that may influence drug efficacy and toxicity.

Role of Single Nucleotide Polymorphisms in Pharmacogenomics (1)
The human genome is composed of around 30000 genes and roughly 3.1 billion nucleotide bases. The 1000 Genomes Project recently sequenced the genomes of 2504 individuals representing over 26 populations groups and reported a total of over 88 million genetic variants, of which 84.7 million are single nucleotide polymorphisms (SNPs), 3.6 million are short insertions/ deletions (indels), and the remaining 60,000 are structural variants.

Although the DNA of two individuals is roughly 99% identical, over 84 million genetic variations occur at the nucleotides level across the human genome. Genetic variants that are found in more than 1% of the population are called polymorphisms. The most abundant type of genetic polymorphisms, which are found in more than 5% of the human population are called common SNPs. It is recognized that roughly 54% of the SNPs are located within the coding region of genes that determine the structure of the gene product (protein). Thus, a sequence variation within these regions may result in alterations in the encoded protein, which in turn may have an effect on phenotypes (e.g., treatment response) (1).

Interindividual Drug Response Variability
Individual responses to a specific drug vary greatly in terms of both efficacy and toxicity. It has been reported that response rates to common drugs for the treatment of a wide variety of diseases fall typically in the range of 50%–75%, indicating that up to half of patients are seeing no benefit. Moreover, many individuals suffer from adverse drug reactions (ADRs). Interindividual variability in drug response affects not only patient well-being, it also poses an enormous clinical and financial burden (2).

Applications of Pharmacogenomics
1. Improve drug safety and reduce ADRs
2. Tailor treatments to meet patients’ unique genetic pre-disposition
3. Identifies optimal dosing
4. Attempts to eliminate the trial-and-error method of prescribing, allowing physicians to take into consideration their patient’s genes, the functionality of these genes, and how this may affect the efficacy of the patient’s current or future treatments (and where applicable, provide an explanation for the failure of past treatments).
5. Decrease the overall cost of health care owing to the reduction in ADRs, number of failed trials, time taken to obtain drug approval, length of medication, number of medications taken, and the effects of disease on the body.
6. Reduce the occurrence of polypharmacy. With tailored drug treatments, patients will not have the need to take several medications that are intended to treat the same condition.
known variants of CYP2D6 can result in a spectrum of activity, from metabolism (including codeine and clozapine, among others). Over 70 CYP2D6 testing has a long-standing evidence of its role in drug metabolism.

Examples of Pharmacogenomics (3)

1. Poor metabolizer are patients with little to no functional metabolic activity
2. Intermediate metabolizer are patients with reduced metabolic activity
3. Extensive metabolizer are patients with normal metabolic activity
4. Ultra-rapid metabolizer are patients with substantially increased metabolic activity

Examples of Pharmacogenomics (3)

Versatile Drug Metabolizer – CYP2D6
CYP2D6 testing has a long-standing evidence of its role in drug metabolism (including codeine and clozapine, among others). Over 70 known variants of CYP2D6 can result in a spectrum of activity, from poor metabolizers who experience adverse effects after accumulation of drugs in the body, to rapid metabolizers who only experience a therapeutic effect when prescribed drugs at a high concentration.

Thrombosis and CYP2C19
Plavix® (clopidogrel), a drug designed to prevent blood clots, presents another case for using genetic testing to select the best course of treatment. Plavix® can have a different impact on protecting stent patients from thrombosis depending on patients’ genetic variance within CYP2C19, which encodes an enzyme that converts the drug from an inactive to an active state. About 25-30% of stent patients have a three-fold risk of stent thrombosis when using Plavix® in comparison to other patients.

Transplantation and CYP3A4*22
Tacrolimus (Tac) is a potent immunosuppressant (with considerable toxicity) given to renal transplant patients to prevent graft rejection. The CYP3A4*22 polymorphism is associated with a significantly altered Tac metabolism and therefore increases the risk of supratherapeutic Tac concentrations early after transplantation. Analysis of this SNP may help in identifying patients at risk of Tac overexposure.

HIV/AIDS and Abacavir
GlaxoSmithKline and Australian researchers have independently developed a pharmacogenetic test for Abacavir (ziagen), a licensed HIV/AIDS drug that causes serious and potentially fatal hypersensitivity reactions in approximately 5% of patients, usually within the first six weeks of therapy.

Breast Cancer and Herceptin
Herceptin (trastuzumab) is a breast cancer treatment that is particularly effective in a subgroup of patients whose tumours express abnormally high amounts of the HER2/neu protein. Up to 30% of breast cancer patients fall into this category, and have a higher incidence of metastasis, drug resistance, and a shorter survival time than patients lacking HER2/neu over-expression. Women with this phenotype who are prescribed Herceptin stay cancer-free 65% longer than those patients on standard chemotherapy. Testing of tumour tissue from women with breast cancer can identify patients who over-express HER2/neu and are likely to benefit from Herceptin.

Irinotecan and UGT1A1
US Food and Drug Administration (FDA) recommends testing for the presence of UGT1A1*28, an allele correlated with decreased transcriptional activity, to predict patients at risk of anticancer drug, irinotecan toxicity. In addition, this polymorphism has been associated with Gilbert’s syndrome, a mild form of an inherited unconjugated hyperbilirubinaemia that does not indicate liver damage but can affect the metabolism of several substances.

Childhood Leukaemia and 6-mercaptopurine
Prescription of 6-mercaptopurine for childhood leukaemia depending on functionality of the TPMT gene, and polymorphisms in neurotransmitter receptor and transporter genes that affect response to certain antipsychotic medications.